

demonstrated to have had coronary artery disease. The simple mean change in coronary artery diameter was about 2%.

The sumatriptan NDA contained 3 angiography studies that measured coronary artery diameters.

In the first study, 18 patients with suspected coronary artery disease underwent angiography, during which they received a 10 minute placebo infusion, after which they were randomized to receive a 10 minute infusion of either placebo (N=8) or sumatriptan 48 mcg/kg (N=10). The C_{max} produced (about 156 ng/ml) was about twice as high as that reported in labeling for a 6 mg subcutaneous dose.

In this study, there was about a 16% mean decrease in coronary artery diameter on drug compared to placebo.

When Dr. Oliva analyzed the data as for the previous studies, the mean maximum decrease in diameter on drug was about 30%, (range 14-50%, with all patients showing a decrease) compared to about 3% for the placebo treated patients (6 patients had no decrease, one had a 10% decrease, one had an 11% decrease).

The second study evaluated a 6 mg subcutaneous dose of sumatriptan in 10 patients undergoing coronary angiography for suspected coronary artery disease. The mean constriction in these patients was about 14%. Interestingly, the mean C_{max} in this study was about 124 ng/ml, compared to the mean C_{max} at this dose of 74 ng/ml described in labeling.

In Dr. Oliva's re-analysis, the mean maximum decrease in diameter was 25% (measured at 10 and 30 minutes after the dose), with a range of 13-60% decrease (all patients had a decrease).

The third study randomized 16 patients with known documented coronary artery disease to sumatriptan 6 mg sc (N=11) or placebo (N=5). The mean decrease in coronary artery diameter was about 9% on drug. As re-analyzed by Dr. Oliva, the mean maximum decrease in the sumatriptan treated patients was about 27% (range 14% to 49% for the 10 patients who had a decrease; one patient had an increase of about 4%) and about 16% for the placebo patients (range 12-22%).

In the Approvable letter, we asked the sponsor to address any potential effects of elevated eletriptan levels that might occur as the result of interactions with 3A4 inhibitors on cardiovascular function. In the verapamil study, the increase in mean diastolic BP AUC (0-12 hr) on eletriptan compared to placebo was about 35 mm Hg, with the same measure for systolic BP being about 20 mm Hg. There were no important effects on mean systolic or diastolic BP (see Dr. Oliva's Table 2, page 8).

An evaluation of Phase 1 studies revealed a dose response relationship for diastolic BP of minor clinical importance, related to Cmax. While BP was monitored in long term studies, it was not measured in a systematic way related to timing of dosing, and while it presents no signal of concern, the data do not speak to effects related to peak plasma levels.

COMMENTS

Several issues, all related to eletriptan's capacity to cause coronary artery constriction, have emerged as a result of the additional analyses performed by Dr. Oliva.

Coronary artery vasoconstriction

Of paramount importance is the finding that there appears to be a drug related decrease in (segmental) diameter of coronary arteries in patients treated with eletriptan. To the extent that this phenomenon is potentially related to decreased coronary blood flow, it is of concern. Of primary concern is the fact that these changes were seen at plasma levels only slightly greater than those achieved with a 40 mg single oral dose. We have no information about the effects on coronary vessels of the plasma levels likely to be achieved if this dose is taken in conjunction with significant 3A4 inhibitors, and certainly no information about the effects of an 80 mg dose, either taken alone or in conjunction with an inhibitor.

At the time of the Approvable letter, we had decided that the application would not be approved if the sponsor could not demonstrate that the risk of concomitant use of eletriptan and important 3A4 inhibitors was unacceptable, even if this concomitant use was contraindicated in labeling. This was based on our belief that labeling could not reliably prevent such use.

We do have considerable clinical experience with the use of an 80 mg single dose, in both short and long-term studies. In this experience, there have been no untoward events that would, in my view, preclude approval of this dose, (especially given my view, discussed later, that there is some evidence that the 80 mg dose may offer an advantage over the 40 mg dose in some patients). One could argue that this experience should serve as support for the conclusion that at least the 40 mg dose can be taken safely in conjunction with an inhibitor that results in a doubling of the plasma levels. However, this experience, while clearly meeting the ICH data requirements, is not sufficiently robust to be able to allay any concerns, **raised by the angiography study**, about the effects of eletriptan on coronary artery constriction, because the angiography study demonstrated constriction at levels only slightly higher than those achieved after a single (uninhibited) 40 mg oral dose. The lack of clinical events in the 80 mg experience is not unexpected, even given the angiographic results, and does not establish that asymptomatic patients are not experiencing coronary artery

constriction. The critical finding here is that coronary artery constriction is seen at plasma levels expected to be seen with the 40 mg dose (or slightly higher), even in the absence of metabolic inhibition.

An important question is whether or not other drugs in the class produce the same degree of coronary constriction as seen here with eletriptan.

As noted by Dr. Oliva, there is no study that directly compares the various triptans. The naratriptan study described above revealed a mean maximum decrease in diameter of about 14%, with an individual maximum decrease of about 18%, compared to 18% and 66%, respectively, for eletriptan. While cross-study comparisons are treacherous, it is interesting to note that the plasma levels of naratriptan in this study were greater than those expected to be achieved at the highest approved oral dose. At the very least, these results raise the question of the relative effects of these 2 drugs, as well as call into question the sponsor's view, based on results of in vitro tests, that eletriptan is considerably more selective for cerebral vessels than naratriptan.

The sumatriptan data are not straightforward.

In the 2 studies that employed a parallel placebo controlled design, the placebo responses differed markedly. In the first (IV) study, there was almost no coronary constriction in the placebo group, while in the third (SC) study, there was a considerable response. In any event, the changes seen in the sumatriptan studies were generally numerically greater than those seen in the eletriptan study, but it is also true that a number of patients in the sumatriptan studies had documented coronary artery disease, again raising the possibility that these patients may be more sensitive than those with normal appearing coronary arteries (the presumed increased sensitivity of abnormal coronary arteries to constriction-inducing agents is a point made by the sponsor's consultant).

Distinctions have been drawn between coronary vasospasm and coronary vasoconstriction, with the implication that it is spasm and not the sort of segmental constriction seen with eletriptan that is associated with variant angina. However, the sponsor has presented no evidence that either the type of constriction (segmental) seen here or the degree of constriction (maximum 66% decrease in vessel diameter) could not result in clinical symptoms. In this regard, it should be recalled that the patient with the maximum decrease experienced chest pain (the sponsor attributed the constriction itself to catheter irritation, but presented no evidence for this conclusion).

Interaction with verapamil and other 3A4 inhibitors

The verapamil interaction study is of great interest in this regard, given that it resulted in unexpectedly high eletriptan levels, given the in vitro data that suggested that verapamil was an intermediate 3A4 inhibitor. The sponsor

suggests that verapamil increases hepatic blood flow (unlike other intermediate inhibitors), which presumably contributes to the unexpected results. However, as demonstrated by Dr. Sunzel, the increase in hepatic blood flow is relatively trivial, especially with multiple dosing, so it is unlikely to be the explanation. This appears to be an example of the discovery of an effect (increased hepatic blood flow) that distinguishes one 3A4 inhibitor from others, which is then postulated to explain unexpected findings, but on closer examination appears unlikely to be important. At the moment, it appears that we do not have an adequate explanation for the results of the verapamil study.

This is of concern, because it suggests that the in vitro data are not reliable predictors of the effect of 3A4 inhibitors on eletriptan levels. One could imagine a scenario in which any one of a number of other "intermediate" inhibitors might result in surprisingly high eletriptan levels by an as yet unknown, and unpredicted, mechanism.

The findings in the verapamil study are also of concern, not only because it casts doubt on the validity of the in vitro tests which currently are used as predictors of effects of these metabolic inhibitors on other drugs, but also because of the specifics of this case; that is, that verapamil is used in a relatively high percentage (about 3% in the NDA database) in this population. The sponsor suggests that verapamil is the **treatment** for coronary vasospasm, and therefore hardly poses a threat in this setting. As Dr. Oliva notes, though, we have no evidence that verapamil is useful in the treatment of eletriptan induced constriction. Also, there are many other 3A4 inhibitors that are available to which these patients may be exposed but which, of course, would not be expected to treat coronary constriction (it does appear, however, that verapamil had the expected effect on blood pressure in the interaction study).

Acceptability of the 80 mg dose

The sponsor is interested in marketing the 80 mg dose. Dr. Oliva has discussed the utility of this dose. I believe that there is some evidence that this dose may offer an increased benefit over the 40 mg dose in some patients (see my memo of 8/17/99, pages 2, 4), although I acknowledge Dr. Oliva's concerns with these data. Further, as noted above, I also believe that there are no signals from the clinical data that would preclude the approval of this dose, although symptoms, including chest pain, are dose related.

However, the overarching concern is the potential of this dose, especially in the presence of metabolic inhibitors (but also when given alone), to result in coronary artery constriction that might result in catastrophic outcomes, albeit outcomes that are expected to be rare.

We discussed our concerns with the sponsor in a telephone call on 11/1/00. In that call, we informed the sponsor that the application could not be approved at this time, until additional data speaking to eletriptan's safety was produced.

Specifically, we asked the sponsor to conduct a study comparing the effects of eletriptan at the highest proposed dose, in the presence of metabolic inhibition, to similar conditions for several of the other available triptans, on coronary artery constriction. Such a study would tell us the relative potency of these compounds on this important measure, information that is now unavailable to us. The current data suggest that eletriptan may have more of a constrictive effect, at plasma levels likely to be achieved, especially in the presence of metabolic inhibitors, than other triptans, although, again, these conclusions are extremely tentative. However, until this question is definitively answered, I see no rationale for making the treatment available.

RECOMMENDATION

Dr. Oliva recommends that the Agency issue a Not Approvable letter. While I agree that the application ought not to be approved until and unless the requested data are submitted and found to be acceptable, and while I agree that a Not Approvable letter can be justified (we have data that at the moment suggests an unacceptable risk), I recognize that a second Approvable letter is also justifiable, and I have no objection to one being issued.

/s/

Russell Katz, M.D.

Cc:

NDA 21-016

HFD-120

HFD-120/Katz/Oliva/Stolzenberg/Fitzgerald/Zarifa/Guzewska/Chen

HFD-860/Sunzel

Note: The 2nd LAB Methods Validation is Pending
(as per Maryja Gurewsky, Chemistry) 12/20/02
Lava Chen, PM
HFD

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Pharmaceutical Analysis

St. Louis, MO

Tel. (314) 539-2011

Ext. 119

FAX Tel. (314) 539-2113

DATE : August 2, 2000
FROM : James F. Brower, Acting Deputy Director, (HFD-920)
SUBJECT: Evaluation of NDA 21-016 Relpax (Eletripan HBr) Tablets
TO : Mona Zarifa, Ph.D., Review Chemist, HFD-120

The evaluation of NDA 21-016 Relpax Tablets has been completed. All methods are suitable for control and regulatory purposes. Problems were encountered with columns and equipment until suitable hardware were obtained. Please refer to specific comments from the evaluating chemist, James R. Marsh, Presented on the attached memorandum and worksheets.

As per program requirements, we are forwarding the original worksheets. We shall retain the reserve sample for 90-days before disposal of remaining sample. If you feel that the reserve sample should be held longer, please contact DTAAD:

^

/S/

/James F. Brower

Acting Deputy Director, DPA HFD-920

Date: February 13, 1998
To: FDA Log
From: Nancy E. Martin
Subject: IND. — - UK-116,044 (eletriptan)
Meeting Minutes - Pre-NDA
Division of Neuropharmacological Drug Products

Executive Summary:

On January 21, 1998, a Pre-NDA meeting was held with the Division of Neuropharmacological Drug Products to discuss specific clinical, statistical and pharmacological issues essential in the preparation and submission of a cohesive eletriptan NDA on September 30, 1998.

Consensus was reached with the Division on the presentation of efficacy and safety data; the adequacy of the eletriptan human hepatocyte induction study results in negating the need for a drug interaction study of eletriptan with oral contraceptives; the format of the clinical and statistical components of the eletriptan electronic submission, and format and content issues concerning the NDA and the NDA Safety Update. To assist Pfizer in the presentation of the eletriptan carcinogenicity data, the Division provided additional written guidance and a diskette with the recommended format and statistical analysis for the eletriptan carcinogenicity data. Discussions with the Division indicate that the eletriptan NDA filing will receive a Standard Review by the Agency. To facilitate our planning efforts for future eletriptan development programs, preliminary guidance was kindly provided by the Division on the eletriptan intranasal, fast dissolving dispersible and dual release formulations.

Participants:

FDA

Dr. Paul Leber, Division Director
Dr. Randy Levin, Clinical Team Leader
Dr. Armando Oliva, Clinical Reviewer
Dr. Glenna Fitzgerald, Pharmacology Team
Dr. Robin Huff, Pharmacology Reviewer
Dr. Nuoyu Huang, Pharmacology Reviewer
Dr. Todd Sahlroot, Biometrics Team Leader
Dr. Qing Liu, Biometrics Reviewer
Dr. Vijay Tammara, Biopharmaceutics Reviewer
Ms. Lana Chen, Project Manager

Pfizer

Dr. Neville Jackson, Global Team Leader
Dr. Verne Pitman, US Team Leader
Dr. Bernard LeBlanc, Toxicologist
Mr. Phil Poole, Global Biometrics Leader
Mr. Scott Haughie, Biometrician
Mr. John Petley, Electronic Submissions
Dr. Ashley Milton, Clinical Pharmacology
Ms. Nancy Martin, Regulatory Affairs

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Draft Labeling

Safety

- *Coronary Safety*

Current US labeling for migraine "triptan" compounds has specific areas of the Contraindications, Warnings and Precautions sections in bold print. Pfizer explored the Division's receptivity to the inclusion of eletriptan coronary safety data in the label as well as their general position on alternative (non-bolded) data presentations in the Contraindications, Warnings and Precautions sections of a label for a "triptan" compound.

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In an effort to investigate the effects of eletriptan upon the coronary artery in man, Pfizer had conducted a study (# 211) of the effect of eletriptan on the coronary artery diameter in ten patients undergoing coronary angiography with normal coronary arteries or stenosis of <50%. A second study (# 309), is to be conducted in forty-five patients undergoing coronary angiography with severe single vessel disease requiring PTCA. These patients will receive either eletriptan, sumatriptan or placebo. The Division did express an interest in this type of data; however, the final decision as to the inclusion of this data in the Contraindications, Warnings and Precautions section of the eletriptan label would be contingent upon the outcome of their review of the data from studies # 211 and # 309.

Although the Division acknowledged its interest in migraine "triptan" compounds for which coronary vasospasm is shown not to be a potential side effect, they noted that this safety profile is extremely difficult for sponsors to prove. They emphasized that to differentiate a compound's coronary safety profile from the rest of the migraine "triptan" therapies, a sponsor would have to provide overwhelming evidence of the compound's safety in a vulnerable patient population. Thus, depending upon the robustness of the safety and efficacy data of a migraine "triptan" compound in such a population, the Division may consider presentation alternatives for the Contraindications, Warnings and Precautions sections of the product labeling; however, the Division made it quite clear that they would strongly object to any promotional use of unsubstantiated safety claims for compounds in this class.

- *Adverse Reactions Presentation*

The eletriptan Phase III clinical program examined the safety and effectiveness of eletriptan in the treatment of three migraine attacks per patient. As a result of this study design, Pfizer proposed that the frequency and distribution of Adverse Events be listed by migraine attack rather than by patient. The Division indicated that their customary practice was to present adverse event data by patient, rather than by migraine attack. Therefore, if an adverse event such as dizziness occurs once during each of the three migraine attacks, it would be counted as one event of dizziness. The Division did suggest that if Pfizer so desired we could present the Adverse Event data both ways, by patient and by migraine attack, in the eletriptan NDA.

Biometrics

- *Proposed Statistical Analyses*

The analysis of the primary efficacy variable (headache response) in the eletriptan clinical program will involve comparisons in headache response rates between eletriptan and placebo and where applicable, between eletriptan and sumatriptan using a step-down procedure. To examine the issues of initial non-response and recurrence, data from a selected group of similarly designed studies (Studies 160-102, 160-104, 160-305, 160-307 and 160-318) will be subject to a prospectively planned meta-analysis, the statistical protocol for which was submitted to the IND on November 1, 1996 (Serial #028) and deemed an acceptable approach by the Division on March 24, 1997. Provided favorable outcomes are achieved in our Phase II/III clinical trials, Agency concurrence was sought on the acceptability of the statistical approach for the proposed wording in the Indications and Clinical Studies sections of the eletriptan label. Although the Division deferred a discussion on data until the actual data became available, it did advise that it would entertain general conclusions.

- *Proposed Eletriptan Efficacy and Safety Tables*

The Division concurred with the draft formats proposed for the eletriptan efficacy and safety tables.

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- *Menstrually Associated Migraine*

The majority of eletriptan Phase III studies collected data on the time relationship of migraine and menstrual period. A statistical analysis of the two hour headache response of migraine attacks associated with menstrual period, combining data across Phase III studies is planned for eletriptan to support a statement in the Clinical Trials section of the label. Although data is not yet available from this analysis, the Division voiced the concern that menstrually associated migraine is a pseudospecific claim which the Division is reluctant to describe in labeling.

Biopharm

- *Drug Interaction Studies*

Based on a review of eletriptan human hepatocyte induction study results, the Division agreed that a drug interaction study of eletriptan with oral contraceptives was not necessary. The Division did request a retrospective subgroup analysis of the database to evaluate the effect of Oral Contraceptives on eletriptan's efficacy, safety and pharmacokinetics.

- *Bioequivalence Studies*

Pfizer verified the completion of bioequivalence studies to demonstrate equivalency of eletriptan clinical and commercial formulations.

- *Electronic Transfer Issues*

The Division requested that the clinical pharmacology study synopses be provided in electronic format and that the pharmacokinetic data sets, inclusive of arithmetic and geometric means be provided in either SAS or Excel. Case Report tabulations for Clinical Pharmacology studies will be confined to patient line listings only.

For the population pharmacokinetics study, the Division requested NONMEN data sets as well as control files and details of the model used in the analysis.

Toxicology

- *Data Presentation*

The eletriptan project team had planned to submit the eletriptan carcinogenicity data in accordance with the FDA's March 12, 1997 Formats and Specifications Guideline for Submission of Animal Toxicology Carcinogenicity Study Data. To facilitate this process, the Division (Dr. Sahlroot) provided additional written guidance (attached) and a diskette on the recommended format and statistical analysis for carcinogenicity data.

- *One Year Dog Study*

The Division also requested a copy of the one year eletriptan dog study and a justification for the doses used in this study and in the six month dog and rat studies relative to human exposure. The inclusion of available toxicokinetic data was suggested for this dose rationale.

Electronic Review

Following up on our October 23, 1997 Pre-CANDA meeting with the Division, Pfizer outlined in the Pre-NDA meeting package specific format proposals in accordance with the FDA's "Guidance for Industry: Archiving Submissions in Electronic Format -NDAs" for the clinical and statistical components of the eletriptan electronic submission.

- *Case Report Forms (CRF)*

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In accordance with 21 CFR 314.50(f)(2), the eletriptan NDA will contain CRFs for each patient who died during an eletriptan clinical study or who did not complete an eletriptan clinical study due to safety reasons. The electronic CRFs will be provided in electronic format only per the Electronic Records; Electronic Signatures regulation (21 CFR Part 11).

- *Clinical Study Reports*

For Phase II/III clinical studies, Case Report tabulations (CRTs) will consist of patient profiles provided as either single PDF files per patient or merged into larger files appropriately bookmarked by either study number or investigator site. Domain profiles will not be required. SAS datasets will be analyzed by JMP and should be accompanied by a variable description similar to PROC CONTENTS. SAS transport was deemed unnecessary.

Clinical study reports will be provided in both electronic and paper format. Pfizer confirmed unique patient identifiers would be supplied to facilitate the identification of patients rolling over from short term efficacy trials to long term safety studies. Suggestions for facilitating access to the study reports in the electronic submission included the provision of the main components of study reports (report text, figures and non-CRT tables) in one PDF with the remaining information in a hypertext linked folder.

Although the Division was receptive to receiving and reviewing examples of proposed electronic formats, they did not foresee a need for an actual demonstration of these submission proposals.

Administrative Issues

- *Investigator Listing and Documentation*

To facilitate a concise eletriptan NDA package, Pfizer proposed that the NDA investigator listing be confined to investigators involved in Phase II and III clinical trials with supportive documentation (CVs) provided for the primary investigator of each clinical site. The Division recommended that the NDA include a complete listing of all investigators and their supportive documentation. The Division forwards this documentation to the Division of Scientific Investigations for the identification and scheduling of FDA audits.

- *NDA Archival Copy*

In accordance with 21 CFR Part 11, the eletriptan Case Report Forms (CRFs) will be provided in electronic format only. As to the other sections of the eletriptan NDA, the Division indicated a preference for an electronic archival copy.

- *NDA Safety Update*

The following information was proposed for the contents of the eletriptan NDA Safety Update:

- Updated safety information (SAEs only) on patients participating in long term open label studies 160-108, 160-316 and 160-317.
- 6 month safety data on adolescents enrolled in Study 160-108 in accordance with the Agency's correspondence of March 31, 1997.
- Blinded safety data (SAEs only) from an ongoing Phase II safety and efficacy study in Japan.
- Safety information from a coronary angiography study (Study 160-309).

Although the Division agreed with the content proposal for the NDA Safety Update, they recommended that the format of the safety summary tables used for the Safety Update include the following three columns: Column 1 would contain the NDA safety data, Column 2 would contain the "new" data accrued between the NDA database cut-off and the safety update database cut-off, and Column 3 would be the total of Columns 1 and 2.

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- *1999 Eletriptan IND Annual Progress Report*

Although the data provided in the eletriptan NDA and Safety Update will encompass the eletriptan safety data generated during 1998, the Division indicated a preference for the standard Annual Progress Report documentation for the 1999 Annual Progress Report for IND. — as opposed to receiving an IND correspondence cross-referencing the NDA /Safety Update data.

Future Eletriptan Development Plans

Nancy E. Martin
RSR

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TO: Nancy E. Martin
Associate Director II
Regulatory Affairs Department
Pfizer, Inc.

FROM: Todd Sahlroot, Ph.D.
Team Leader
Division of Biometrics 1 (HFD-710)

Roswitha Kelly, M.S.
Preclinical Review Coordinator
Division of Biometrics I (HFD-710)

George Chi, Ph.D.
Director
Division of Biometrics I (HFD-710)

TOPIC: Needed carcinogenicity data analyses for IND — eletriptan

DATE: January 21, 1998

For expedited statistical review of this application's preclinical carcinogenicity data please provide the following:

(1) **Study Design:** Fully describe the design for each study including: strains of rodents, route of administration, time of interim and terminal kill, the number of animals used per dose group, and the type of control used (e.g., vehicle only).

(2) **Needed Statistical Analyses:**

Note: All analyses should be performed for each sex separately.

[A] **Survival:** Please provide trend tests, adjusted Cox and Kruskal-Wallis testing, all pairwise comparisons of all groups (with adjusted Cox and Kruskal-Wallis), and Kaplan Meier survival curves. See references (1), (2), and (3). Weigh doses by the actual dose levels used.

[B] **Tumor Analysis:** Use Peto's survival-adjusted trend tests appropriate for fatal, incidental and palpable tumors (reference (4)). Use the actual doses as weights. We suggest using fixed time intervals, e.g., weeks 0-52, 53-78, 79-91, 92-104, and terminal sacrifice. Perform exact permutation trend tests (e.g., StatXact software, reference (5)) and asymptotic tests when

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combined fatal and incidental tumors fall in the same time interval or when the number of tumors is very large. Pairwise comparisons between high dose and control are optional. Statistical significance levels to be used are 0.025 for rare tumors and 0.005 for common tumors. If other levels are chosen (e.g., Westfall-Young), justification for the choice needs to be provided. Certain tumors should be also grouped and then analyzed. Please refer to reference (9).

[C] If a study shows no tumorigenic effect (for a given species and sex), please document the validity of the study (references (6), (7), and (8)) establishing that there were enough animals exposed for a sufficient length of time for late developing tumors to manifest and that the high dose represents a reasonable tumor challenge.

(3) For guidance we are providing the following materials:

[A] A representative statistical review of carcinogenicity studies which can be used as a model for presenting analytic results in a statistical report.

[B] Several internal SAS programs (still in the development stage) which can be used as a framework for your analytic approach.

(4) **Data format:** In addition to the needed statistical report of analytic results, please provide all animal data in 'STUDIES' format or in the old 'OEB' format according to reference (10).

REFERENCES:

- (1) Cox, D. (1972). Regression models and life tables, *Journal of Royal Stat. Soc. B*, 34, 187-200.
- (2) Gehan, E. (1965). A generalized Wilcoxon test for comparing arbitrarily singly censored samples, *Biometrika*, 52, 203-223.
- (3) Thomas, Breslow, and Gart (1977). Trend and homogeneity analyses of proportions and life table data, *Computers and Medical Research*, 10, 373-381.
- (4) Peto et al. (1980). Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, long term and short term screening assays for carcinogens: A critical appraisal, *International Agency for Research Against Cancer Monographs, Annex to Supplement*, WHO, Geneva, 311-426.

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- (5) StatXact-3 for Windows (1996). Statistical Software for Exact Nonparametric Inference, Cytel Software Corporation, Cambridge, Massachusetts.
- (6) Haseman (1984). Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol. 58, 385-392.
- (7) Chu, Cueto, Ward. (1981). Factors in the evaluation of 200 National Cancer Institute carcinogen bioassays, J. Of Toxicology and Environmental Health, Vol. 8, 251-280.
- (8) Bart, Chu, Tarone. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity, J. Of the National Cancer Institute, 62, 957-974.
- (9) McConnell, Solleveld, Swenberg, Boorman (1986). Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies, J. Of the National Cancer Institute, 76, 283-289.
- (10) Lin (1997). Formats and Specifications for Submission of Animal Carcinogenicity Study Data, OEB document.

In case of questions, the contact person is Ms. Kelly, (301)827-1547.

cc: HFD-024/Dr. DeGeorge
HFD-120/Drs. Fitzgerald, Huff
HFD-120/Ms. Chen, CSO
HFD-710/Drs. Sahlroot, Chi
HFD-710/Ms. Kelly
HFD-710/file

MEMORANDUM

DATE: August 17, 1999

FROM: Acting Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-016

SUBJECT: Recommendation for Action on NDA 21-016, for the use of Relpax (eletriptan hydrobromide) in the acute treatment of migraine

NDA 21-016, for the use of eletriptan, a 5HT_{1B/1D} agonist, for the acute treatment of migraine, was submitted by Pfizer and received by the Agency on 10/27/98. The NDA contains the results of 8 placebo controlled trials (7 in adults, 1 in adolescents), all of which primarily evaluated the effects of a single dose of eletriptan on the relief of pain at 2 hours post-dose. Specifically, efficacy was assessed by the proportion of patients with moderate or severe headaches at baseline who achieved no or mild pain at 2 hours after dosing. Of the 7 studies in adults, 2 evaluated 20, 40, and 80 mg single doses, 4 studies evaluated 40 and 80 mg single doses, and 1 study evaluated just a 40 mg dose. In the latter study, patients who did not respond at 2 hours to a 40 mg dose were re-randomized to 40, 80, or placebo for a second attack. In addition, 3 of the dose response studies included various doses of oral sumatriptan as comparators in addition to placebo. In the study in adolescents, only the 40 mg dose was evaluated. A total of over 6000 patients were randomized to treatment in these trials, and the NDA contains safety experience in over 5500 unique individuals who received at least one dose of eletriptan.

The primary review of the safety and effectiveness data was performed by Dr. Armando Oliva (review dated 7/9/99) and the statistical review was performed by Dr. Paul Flyer (review dated 8/5/99). Dr. Randy Levin, Neurology Team Leader, has written an overview of the relevant data (memo dated 8/5/99). Dr. Rae Yuan of the Office of Clinical Pharmacology and Biopharmaceutics has reviewed the pharmacokinetics and metabolism data (review dated 8/9/99). In this memo, I will offer my recommendations for action on this NDA.

EFFECTIVENESS

As noted by all reviewers, there is overwhelming evidence that eletriptan is effective, as judged by the usual standards, in the treatment of acute migraine headaches. All doses tested in the studies described above were statistically significantly superior to placebo. One study, not described above, evaluated the effects of 5 mg, 20, and 30 mg doses. The 5 mg dose was slightly numerically superior to placebo (38% vs 34% 2 hour response rates, respectively) but not significantly different from placebo at ($p=0.5$; N =about 90/group).

In 5 of the 6 studies which directly compared 40 mg to 80 mg, the response at 80 was numerically superior to that at 40 mg (ranges from 3-14% greater response rate) but not statistically superior. A pooled analysis of the 7 controlled trials in adults yielded a nominally significant dose response ($p=0.0001$), with the comparisons for response rate between 80 vs 40 mg and 40 vs 20 mg each reaching nominal significance (see Dr. Oliva's review, page 28, Table 20). In the one study described above in which patients who did not respond to a 40 mg dose were re-randomized for a second headache, there was no difference between the response rate between the 2 doses for the second headache.

The sponsor also performed a pre-planned meta-analysis of 5 of the trials in an attempt to assess the effectiveness of a second dose in those patients who did not respond at 2 hours, as well the effects of a second dose on recurrence in patients who did respond at 2 hours. The former analysis did not distinguish drug from placebo, but the latter analysis suggested that a second dose in responders did decrease the frequency of recurrence.

As noted above, 3 studies compared eletriptan to sumatriptan.

In study 104, patients were randomized to either eletriptan 40 or 80 mg, sumatriptan 25 or 50 mg, or placebo. In Study 314, patients were randomized to either eletriptan 20, 40, or 80, sumatriptan 100 mg or placebo, and in Study 318, patients were randomized to either eletriptan 40 or 80 mg, sumatriptan 50 or 100 mg, or placebo. Dr. Oliva presents the results of the various comparisons in his review (pages 26 and 27, Tables 17 and 18). Eletriptan 80 mg was consistently superior to all doses of sumatriptan at 2 hours, with these differences being nominally statistically significant; the results were less consistent with the 40 mg dose.

SAFETY

As noted earlier, about 5500 unique individuals received at least one dose of eletriptan. The number of individuals who received chronic treatment (defined as treating an average of 2 or more headaches/month) for at least 6 and 12 months was considerably less extensive:

	6 months	12 months
40 mg	212	96
80 mg	272	108

Deaths

A total of 4 patients assigned to eletriptan died during the development program. One of these deaths occurred in a patient receiving eletriptan but in a trial that is still otherwise blinded. As reported by Dr. Oliva, (page 48 of his review), the mortality (excluding this latter patient) was slightly less for eletriptan compared to sumatriptan. Two of the deaths were suicides, both in patients with a history of depression, both who had taken 20 mg

prn for between 10 weeks and 9 months. In one, the suicide occurred 4 days after her last dose, in the other 55 days after her last dose.

A 45 year old woman died of a hemorrhagic cerebral infarction 2 weeks after drug was dispensed. However, it is unknown if drug was ever administered.

Serious Adverse Events

The rate of serious adverse events was comparable between eletriptan and sumatriptan, and was somewhat greater on placebo, although the person-year experience on placebo was considerably less than on eletriptan.

Serious events of note included:

A 54 year old woman who participated in a coronary angiography study (N=10) developed chest pain and a 60-70% constriction of the right proximal coronary artery. The constriction lasted 30 minutes, but the pain persisted and did not respond to glyceryl trinitrate. There were no EKG changes. The sponsor concluded that the constriction was related to catheter tip irritation, and that the pain was unrelated to the constriction. The plasma level achieved in this study was similar to that seen after a 40 mg dose.

A 50 year old woman developed elevated ALT (304-ULN23) and AST (129-ULN19) after 4 doses of 80 mg taken over 23 days. These changes resolved over 2 weeks. Four other patients (all taking multiple 80 mg doses) had elevated LFTs without increased bilirubin.

Other Adverse Events

Eletriptan use was associated with the typical events associated with other triptans. Many of the ADRs were dose related. Of interest is the incidence of chest pain, which revealed the following dose response (these are incidences after the initial dose in controlled trials):

	20mg (N=531)	40mg (N=2138)	80mg (N=1518)	Placebo (N=1235)
Chest pain	0.9%	2.4%	4.7%	1.2%

In the 3 studies in which sumatriptan was a comparator, the following incidences of chest pain were seen after the initial dose (taken from Dr. Oliva's Table 54, page 59):

	Eletriptan			Sumatriptan			Placebo
	20 mg	40 mg	80 mg	25 mg	50 mg	100mg	
N	144	495	485	180	362	298	319
	0.7%	1.8%	4.7%	0.6%	1.4%	1.3%	1.6%

METABOLISM -

The primary route of metabolism of eletriptan is through CYP3A4. While the sponsor did not extensively evaluate interactions with a range of 3A4 inhibitors, an interaction study with erythromycin was performed, which increased the C_{max} of eletriptan 2 fold, and the AUC 4 fold. In an in vitro study with ketoconazole, eletriptan metabolism was inhibited by about 70%. According to Dr. Yuan of OCPB, interactions with potent 3A4 inhibitors could be expected to result in substantial increases in eletriptan plasma levels.

COMMENTS

The sponsor has submitted the results of 7 controlled trials in adults which clearly demonstrate the effectiveness of single doses of either 20, 40, or 80 mg of eletriptan as an acute treatment of migraine headaches. There is some evidence that response is dose related, although in no single study is there a statistically significant superiority of the 80 mg dose compared to the 40 mg dose (as noted above, a meta-analysis did yield a significant difference between 80 and 40, and between 40 and 20).

Three trials included sumatriptan arms, and, in general, the 80 mg dose of eletriptan was consistently superior to even the 100 mg dose of sumatriptan.

The application also contains safety data for over 5500 unique individuals exposed to at least 1 dose of eletriptan. The number of patients exposed chronically to the 80 mg dose falls slightly short of the ordinarily required 300 patients for 6 months, as does the number of patients exposed to the 40 mg dose. Of interest, 1 patient experienced chest pain and a 60-70% constriction of a coronary artery during an infusion/angiography study; the pain persisted beyond the duration of the visible constriction, did not respond to dilators, and was accompanied by a normal EKG throughout. Several other patients experienced elevated LFTs after multiple 80 mg doses. In general, ADRs were dose related. In particular, the incidence of chest pain was clearly dose related, and was considerably greater on eletriptan 80 mg than on sumatriptan. In my view, though, there is no signal of risk in this experience that would preclude approval, even of the 80 mg dose (although, as noted the chronic experience at this dose is minimal).

However, of particular importance is the fact that CYP3A4 is the primary metabolizing enzyme of eletriptan. Although the sponsor did not adequately evaluate the metabolic fate of the drug, it is clear that interaction with 3A4 inhibitors will result in elevated eletriptan levels. It is likely that interaction with potent inhibitors will markedly increase levels.

Although there is no definitive evidence that eletriptan, even at 80 mg, is associated with serious cardiac toxicity, there is a general presumption that all members of this class, absent compelling evidence to the contrary, are capable of constricting coronary arteries,

sometimes resulting in myocardial ischemia, with potentially serious, or even life-threatening consequences. The rate of such drug related events is unknown, but it is considered relatively rare, and the absence of any such events in a typical drug development cohort for such a drug does not establish it is free of this risk. In the eletriptan cohort, for example, we can be 95% confident that the true rate of such an event is no greater than 1 in about 1800 patients (assuming that no cases were seen, which is open to question). Indeed, the incidence of chest pain at the 80 mg dose was about 5%, which was greater than that seen with sumatriptan. Of course, it is impossible to know with certainty if any of these events were anginal, given that there were no EKGs done at the time of the event (in this regard, the absence of any significant findings on the EKGs performed routinely in these studies is of little value, given that none were taken at the time of, or shortly after, dosing).

In any event, I am aware of no evidence that supports the view that eletriptan is free of the potential risk of cardiac events associated with other triptans. Given this, and given the presumption that there is a relationship between plasma level (in particular, probably Cmax) and this potential risk, the fact that eletriptan is metabolized by CYP 3A4 is worrisome. The number of available 3A4 inhibitors is relatively great, and there is little data in the application that speaks to the increase in eletriptan levels that will result when it is given with various of these inhibitors. We do know, though, that concomitantly administered erythromycin increases the Cmax of eletriptan 2 fold, and the AUC 4 fold. It is presumed that a potent 3A4 inhibitor may increase the levels up to perhaps 8 fold, compared to when eletriptan is given alone.

Given the relative ubiquity of 3A4 inhibitors, their potential effect on eletriptan levels, and the presumed relationship between eletriptan levels and risk for cardiac events, it is reasonable to conclude that concomitant use of eletriptan and 3A4 inhibitors should be avoided. At first blush, approving the application with labeling that contraindicates this concomitant use might appear reasonable.

In my view, though, such labeling cannot reliably prevent this concomitant use. We are aware, of course, of several recent examples of drugs in which labeling, despite explicit and prominent warnings of serious adverse events, did not prevent their misuse, with sometimes disastrous consequences. Further, although completely conjecture, the intermittent use of eletriptan may be considered to make the risk for inappropriate concomitant use with 3A4 inhibitors even greater than if it were taken chronically. Specifically, one might presume that patients and prescribers alike may be more attentive to inappropriate combinations when both drugs are given chronically; when one drug is used infrequently, like eletriptan, it is easy to "forget" that a patient is actually "taking" the drug. In such a scenario, a patient may be prescribed a course of, for example, ketoconazole, and then happen to have a migraine during this course of treatment. It is easy to imagine such a patient administering eletriptan without considering the potential risk.

If there were a compelling reason to have eletriptan available, the risk of potentially dangerous interactions might be acceptable. Such compelling reasons might include that

it is intended to treat a serious illness with few treatment options, or even perhaps that it offers a clear benefit compared to other available treatments. Although there is no doubt that a migraine headache is uncomfortable, painful, disruptive, unpleasant in the extreme, and even acutely debilitating, it is not ordinarily a serious or life-threatening condition, and, in any event, there are a number of available treatments for it, including a number of other triptans which presumably work by essentially the same mechanism. Importantly, no available triptan is metabolized via 3A4.

Further, I am aware of no evidence that clearly establishes the superiority of eletriptan to other available treatments. While 3 of the controlled trials in the application included sumatriptan arms, and, in general, the 80 mg dose of eletriptan seemed to be consistently significantly superior to even the 100 mg dose of sumatriptan, there were problems with these studies, as noted by Dr. Levin in his memo. In one 2 center study, there was a treatment by center interaction, related to the fact that in one center sumatriptan was not distinguished from placebo. In another study, patients who had previously failed on sumatriptan were permitted to be enrolled. Even if there were no problems with these studies, however, the outcome would not establish the superiority of eletriptan to treatments other than sumatriptan. Indeed, the studies do not even establish eletriptan's superiority to sumatriptan definitively, since a comparison to the highest available subcutaneous dose of sumatriptan might have had different results. The incidence of adverse events was greater on eletriptan (at least at 80 mg) than with sumatriptan 100 mg.

A potential alternative to not approving the application would be to approve only the lowest dose shown to be effective, 20 mg. There is no reason to believe that warnings in the label would be heeded more frequently in this case, of course, but the case could be made that interactions with potent 3A4 inhibitors and eletriptan at this low dose might result in acceptable plasma levels of eletriptan. However, in such circumstances, we still might expect plasma levels to be reached that exceed those associated with the 80 mg dose given alone, and we have little to no experience in the application that speaks to the safety of such exposures.

**APPEARS THIS WAY
ON ORIGINAL**

In summary, while the sponsor has submitted substantial evidence of effectiveness for eletriptan as an acute treatment for migraine headache, and there is no affirmative evidence of toxicity that would preclude approval, the fact that eletriptan is primarily metabolized by CYP3A4 creates a risk for producing markedly elevated levels of the drug, the safety of which have not been adequately evaluated. The risk is of great concern because eletriptan is a member of a class of compounds accepted to have a small, but finite, risk of coronary artery constriction, which may have serious consequences. While labeling might adequately warn of this risk, there are serious questions about the ability of labeling to adequately prevent inappropriate concomitant use of eletriptan and 3A4 inhibitors. In my view, as discussed above, there are no compelling reasons that would justify this risk. For these reasons, I recommend that the application not be approved.

^
/S/
v

Russell Katz, M.D.

Cc:
NDA 21-016
HFD-120
HFD-120/Katz/Levin/Oliva/Fitzgerald/Chen

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: August 6, 1999

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 21-016
Relpax™, eletriptan hydrobromide
20 and 40 mg tablets of base

SUBJECT: Pharmacology/Toxicology Team Leader Memo

Eletriptan is another of the triptan series (there are four marketed drugs: Imitrex, Zomig, Amerge and Maxalt) that is indicated for the acute treatment of migraine with or without aura in adults. Unlike the other drugs in the class, eletriptan is metabolized primarily by CYP3A4, and it has been demonstrated that inhibitors of that enzyme (including some SSRIs, antifungals, antimicrobials, proteinase inhibitors, certain calcium channel blockers, and grapefruit juice) increase plasma concentrations significantly.

The pharmacology and toxicology studies which were submitted to the NDA are adequate to support an approvable action. It should be noted for the record that the toxicology package does not provide a robust workup. The chronic toxicity studies (6 month rat and dog and 12 month dog) were all conducted at doses that caused relatively minor toxicity and undoubtedly the doses could have been higher. However, by the time a drug has reached the NDA stage, clinical experience replaces the routine toxicology studies for purposes of predicting potential toxicities. Therefore, repeating those studies would not be warranted. The reproduction studies were also designed to use relatively modest doses, but the teratology and pre- and postnatal studies did produce effects which are reminiscent of other drugs in the class (decreased fetal and pup weights and fetal structural abnormalities) so they can be considered acceptable. These effects were observed at exposures that represented low multiples of the clinical exposure (based on two 40 mg. tablets/day), and the no-effect exposures were equal to or marginally higher than the clinical exposure. Doses in the rat fertility study were too low, however, to produce even minimal toxicity. Because a large proportion of migraine patients are women of childbearing potential, and because effects on fertility cannot be examined in humans, that study should be repeated using doses which are associated with some degree of toxicity. The carcinogenicity studies, on the other hand, did use adequate doses, and the high dose in rats probably exceeded the MTD. It was noted during the review of the NDA that the pre- and postnatal study did not include an assessment of memory and learning in the F1 pups. The sponsor was notified of this on January 27, 1999 and asked to conduct a modified study which examines just those

parameters. That study was begun on March 9, 1999, and is presumably completed at this time.

The recommended revised labeling for the toxicology sections is attached to this memo. The recommended Mechanism of Action labeling has also been revised and should appear as it does in the action letter. We have made a major change in the sponsor's pregnancy label, changing it from Category B to C, based on fetal effects our reviewers consider to be drug-related, but which were not noted by the sponsor.

Recommendations:

This NDA is approvable for pharmacology and toxicology with the attached labeling as long as the sponsor agrees to the following:

- 1) Submit the results of the study which examined effects on learning and behavior in F1 rat pups prior to final approval.
- 2) Commit to initiating a rat fertility study as soon as possible in which adequately high doses are studied. The final report may be submitted in Phase 4.

Attachment
NDA 21-016
cc. Div. File

Katz/Levin/Oliva/Huff/Fisher/Chen/Fitzgerald

/S/

Glenna G. Fitzgerald, Ph.D.

2 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: August 5, 1999
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 21-016, Relpax (eletriptan)
To: file

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Background

Pfizer submitted NDA 21-016 for Relpax (eletriptan hydrobromide), a 5 HT_{1B/1D} agonist, for the acute treatment of migraines with and without aura in adults. IND for eletriptan was submitted in December of 1994. We received the NDA on 10/27/98. Eletriptan is not currently marketed in any country.

CMC

The CMC section was evaluated by Drs. Zarifa and Guzewska. The reviewers concluded that there were no CMC issues that precluded approval.

Comments

The sponsor proposes marketing a 20, 40 and 80 mg tablet.

Nonclinical pharmacology and toxicology

The animal studies were reviewed by Drs. Robin Huff and Glenna Fitzgerald. I did not have Dr. Fitzgerald's memo at the time of this memo but I did discuss the issues with her. She concluded that prior to approval, the results of the peri and post natal studies assessing learning and memory be assessed. In addition, she also requested that the sponsor commit to initiating a rat fertility study at appropriately high doses as soon as possible. Labeling changes were recommended.

Comments

The mechanism of action is similar to other triptans. The sponsor notes that the drug is more selective for reducing carotid blood flow versus coronary artery diameter than sumatriptan. Our reviewers note that the difference is slight and the maximal vasoconstriction is similar for both drugs. The N-desmethyl metabolite exhibits vasoconstrictive properties similar to eletriptan.

In the chronic tox studies, the doses of the rat and dog study did not approximate the MTD. The short term studies provide evidence that the animals could have tolerated doses many times higher than the ones used in the chronic studies. Even the drug exposures for the high doses were similar to or not much greater than that for humans at the sponsor's proposed maximum dose of 160 mg/day. The AUC achieved in the high dose dog study was less than the AUC achieved with the proposed 80 mg x 2 dose in humans. The Cmax in the 12 month study was 1.4 times the Cmax for the 80 mg dose in the human study.

In toxicology studies, there was evidence for a dose related increase in heart rate and BP. Repeat dose tox studies showed increase liver weights with centrilobular hypertrophy at doses of 25 mg/kg and above. Thyroid follicular hypertrophy was seen at doses of 5 mg/kg and above. Corneal opacities were seen in the dogs at 1 month but not at 6 and 12 month studies. Mild myocardial fibrosis was diagnosed in 2 dogs at 5 mg/kg after 1 month and 1 dog at 7.5 mg/kg after 2 weeks. In the 6 month study, 1 of 8 dogs at the 2.5 and 5 mg/kg dose had chronic peptic ulcer disease thought to be related to the use of a dry powder formulation. It was not seen in the 12 month study where the tablet was used.

No mutagenic, genotoxic or teratogenic effects were observed in the studies. The carcinogenicity studies were negative. The doses used in the carcinogenicity study were

acceptable. The doses of the developmental and reproductive toxicity were too low in the opinion of the reviewers. The exposures were only 1.4 to 2.8 times that seen in humans given 80 mg x 2. -

The sponsor started (3/9/99) a peri and post natal study evaluating the effects of learning and memory. The results, which are usually provided with triptan drugs, were not in the NDA. These studies are of particular importance given the population being treated.

Human pharmacology and bioavailability and bioequivalence

The PK studies were evaluated by Drs. Rae Yuan, Joga Gobburu and Chandra Sahajwalla. I did not see a completed review at the time of completion of this memo. My conclusions are based on information from draft reviews, discussion with the reviewers and participation in a meeting with the biopharm team. The reviewers did not find any unresolved issues that precluded approval but several issues were raised in reference to labeling including the consequences of the drug being metabolized by CYP3A4.

Comments

The drug is mostly metabolized with only 10% of the renal excretion attributed to the parent. The major metabolic pathway is by CYP3A4. The metabolite, UK 135,800, has vasoconstrictive properties in animals similar to that seen with the parent. It was not fully evaluated and was not measured in the phase 2/3 studies. It was determined that the metabolite has a prolonged half life of around 12 hours. The drug does not have linear kinetics over the proposed dose range. This is converse the sponsor's conclusion that the kinetics were linear. Eletriptan is 85% protein bound. The T_{max} is 1.5 hours and the half life is 4 hours. There was no effect on the PK of the drug based on age, gender, and renal function. Drug levels were increased with hepatic impairment, food, propranolol use and erythromycin use.

In regards to eletriptan metabolism by CYP3A4, the only specific interaction study was with erythromycin, a moderate 3A4 inhibitor. In this study, there was a 4.5 fold increase in the AUC and a 2 fold increase in the C_{max} of the parent drug. The other inhibitors were not evaluated except using population PK analyses. The population PK studies were not thought to be valid by the reviewers because of the small number of patients involved and the use of saliva, not plasma, levels as a measure of exposure. The use of saliva levels were a problem because they were not adequately linked to plasma levels. The reviewers concluded that CYP3A4 inhibitors are likely to lead to increases in the plasma levels and appropriate wording should be added to labeling.

The sponsor found a 30% increase in AUC and a 25% decrease in clearance in subjects with mild to moderate hepatic impairment but failed to study subjects with severe liver impairment.

The 0.02% of a single dose of the drug passes into breast milk. The time course of the levels of the drug or its active metabolite were not studied. The reviewers could only estimate that at approximately 48 hours following use of a single dose, the breast milk would not contain drug or metabolite.

There was an increase in the AUC by about 33% when given in patients on propranolol.

Population PK studies did not provide sufficient numbers of patients to evaluate many of the covariates. As previously mentioned, these studies also used saliva concentrations which are of limited values since they were not linked to plasma levels.

Efficacy

The efficacy data was reviewed by Dr. Armando Oliva with a statistical consultation from Dr. Paul Flyer. These reviewers concluded that the sponsor demonstrated in more than one adequate and well controlled study that eletriptan was an effective acute treatment for migraines. The studies did not provide adequate evidence to support claims that the drug is superior to sumatriptan or that the 80 mg dose is superior to 40 mg.

Comments

The sponsor conducted 4/8 outpatient studies to evaluate the efficacy of eletriptan. The studies addressed issues not only related to the question of the efficacy for the acute treatment of migraines but also other issues like the efficacy of a second dose for persistent or recurrent migraines, comparisons with sumatriptan, benefit of 80 mg for people failing on 40 mg. Some of the efficacy questions are discussed below.

Is eletriptan effective for the acute treatment of migraine?

The evidence from the controlled clinical trials provide sufficient evidence to support the conclusion that eletriptan is an effective acute treatment for migraine.

The sponsor conducted 8 (102, 103, 104, 105, 305, 307, 314, 318) studies with an adequate design to assess the efficacy of the drug for the acute treatment of migraines. Each of these studies randomized patients with a migraine with moderate to severe pain in a double blind fashion to placebo or drug for treatment of their headaches as outpatients. Headache response rates 2 hours following treatment were based on the percentage of patients with a reduction of pain to mild or no pain. The sponsor evaluated doses of 20, 40 and 80 mg. All studies evaluated 40 mg and 80 mg for the initial attack except for study 103 and 105 which only evaluated 40 mg. Only 2 studies evaluated 20 mg (102 and 314). All studies enrolled adults except for Study 105 which only involved adolescents.

All of the studies in adults showed a statistically significant increase in headache response at 2 hours in patients randomized to drug compared to those randomized to placebo. This is in contrast to the study in adolescents which did not show any difference between groups. The results are summarized in the table below.

2 hour headache response rates (N) (*p value < 0.05, #adolescent study)				
Study	Placebo	20 mg	40 mg	80 mg
102	24% (126)	47%* (273)	62%* (281)	59%* (290)
103	30% (122)	NA	62%* (492)	NA
104	40% (86)	NA	62%* (175)	70%* (170)
105#	57% (133)	NA	57% (141)	NA
305	19% (432)	NA	62%* (430)	65%* (446)
307	21% (102)	NA	54%* (206)	68%* (208)
314	24% (126)	54%* (129)	65%* (117)	77%* (118)
318	31% (80)	NA	64%* (169)	67%* (160)

The evidence for efficacy is supported by a decrease incidence of associated symptoms in adult patients treated with eletriptan compared to placebo. While these symptoms were not primary outcome measures, the differences with placebo were associated with a nominal p value of < 0.05 in most comparisons.

What are the effective doses?

All doses evaluated in the outpatient studies, 20, 40 and 80 mg, were effective. There is some evidence to suggest that the higher doses may be more beneficial but there is little evidence to suggest that the 80 mg is better than the 40 mg dose.

Numerically, the 20 mg dose had a smaller response rate than the higher doses but the findings were not statistically different. There was a difference in the headache response rates seen with 20 and 40 mg of 11 and 15% in the two studies in which both doses were used. Numerically, the differences between the 40 and 80 mg doses were somewhat inconsistent and statistically not significant across studies. In the 6 studies where the two doses were studied together, the differences in 2 hour response rates between 40 and 80 were -3, 8, 3, 14, 12, 3%, respectively. The response rates for the 40 mg dose ranged from 54 to 64% (average 61%) compared to a range of 59 to 77% (average of 66%) for the 80 mg dose. Recurrence rate for the 40 and 80 mg group was 23 and 21%, respectively.

In addition, the 80 mg was not effective in patients who did not benefit from 40 mg. In study 103, the sponsor specifically evaluated the effectiveness of 80 mg in patients who failed 40 mg. The 2 hour headache response rates were 20 and 26% for the patients treating a second headache with 40 and 80 mg, respectively. This difference was not statistically different. The sponsor claims that patients in the long term studies preferred 80 mg over 40 mg. The sponsor bases this information on an interim analysis for which we do not have data.

Doses of 5, 20 and 30 mg were evaluated in study 302 where patients treated their headache in the clinic. The response rate for the 5 mg dose was not different from

placebo (p value of 0.52) whereas a dose of 20 and 30 mg in the same study were associated with p values of 0.065.

Should patients take a second dose of eletriptan if the headache does not respond or if it reoccurs?

The sponsor evaluated the headache response 2 hours following a randomized second dose of drug. The results suggest that a second dose may be effective if the headache reoccurs after an initial response but not if the initial dose is ineffective.

For recently approved acute treatments for migraine, labeling notes that additional doses of drug can be taken if headaches do not respond to the initial dose or reoccur. These recommendations have been based on the safety of additional doses and not on results from randomized efficacy studies. This differs from eletriptan where the sponsor has studied this effect by randomizing patients to drug or placebo for the treatment of recurrence or persistent headaches. Combining the results of about 350 patients in 5 studies who had headache reoccurrence, the 2 hour headache response rate following treatment with a second dose shows a difference in favor of drug over placebo associated with a nominal p value of < 0.05 . The rates for the 40 and 80 mg dose were 74 to 82% compared to 28 to 33% for placebo.

This is in contrast to a second dose for persistent pain where no difference between treatment with drug and placebo was found. The sponsor combined all patients, around 950, who had moderate or severe pain 2 hours after treatment from the 5 studies where the second dose was assessed. In a comparison of the 2 hour response rates, there was essentially no difference in response rates in the patients assigned to placebo or drug.

Is treatment with eletriptan better than with sumatriptan?

The sponsor has conducted three studies comparing the two drugs. There was evidence to suggest that the 80 mg dose of eletriptan has a less favorable safety profile with more adverse events than sumatriptan. There differences in efficacy measures between drugs was generally in favor of 80 mg of eletriptan. The evidence was not suggestive of a difference between 40 mg and sumatriptan. The findings do not appear to justify the conclusion that one treatment is more beneficial than the other.

Some of the problems with the comparisons are noted below. In study 318, the response rates were higher in the 80 mg group compared to sumatriptan but the adverse event profile seemed to favor sumatriptan. In study 104, there was no difference between the 40 mg dose of eletriptan and the 50 mg dose of sumatriptan. The difference between the 80 mg dose and 50 mg dose favored eletriptan at a nominal p value of 0.05. This was in the face of a treatment by center interaction. In this two center study, one center numerically sumatriptan did better than eletriptan in contrast to the second center, where there was only a small difference between sumatriptan and placebo. The design of study 314 was flawed as it allowed sumatriptan non responders to be enrolled. The response rate for the 80 mg group was higher than in the patients treated with 100 mg of sumatriptan with a

associated p value of < 0.05 . The difference with the 40 mg dose was associated with a p value > 0.05 . Another problem with this study was that the outcome measure was changed from showing equivalency to showing superiority only after the sponsor determined the results from an interim analysis.

Is eletriptan effective for adolescents or the elderly?

Eletriptan was not shown to be effective in adolescents or in the elderly. The only study evaluating the efficacy in adolescents suggested that the drug is not effective in adolescents. There was essentially no difference in response rates for patients treated with 40 mg of drug and placebo. The response rates were 57% for both groups. Other doses were not studied. Patients over the age of 65 were not specifically studied. There were only 35 patients enrolled in the efficacy trials over the age of 65. Only 5 patients were on placebo and they had a response rate of 71%.

Does eletriptan prevent migraines?

In study 306, the sponsor evaluated the effect of 80 mg to prevent migraines when used at the time of aura. There was no significant differences between groups.

Conclusion

In many ways, the evaluation and results for eletriptan are similar to all of the recently approved triptans and should have similar descriptions in labeling. The indication is for the acute treatment of migraines with and without aura in adults. As with all recently approved acute treatments of migraines, we should describe all of the adequate and well controlled studies performed in outpatients including the headache response rates at 2 hours. There are 8 studies to be described. We should include the statement on the associated symptoms. We should include the Kaplan Meier curves for the time to headache response and time to rescue for all of the adult studies. In the dosing section, effective doses include 20 and 40 mg without evidence for increased benefit and possible greater adverse events with higher doses (see safety review below). There is insufficient in the elderly to determine if the drug is effective.

In some ways, the evaluation has been different than other recent triptans. There is evidence that the drug does not work in adolescents. There is evidence that a second dose of the drug does not work without an initial response but can be helpful with reoccurrence. The efficacy of the drug was not shown to be better than sumatriptan at doses with a similar adverse event profile.

Safety

The safety data was reviewed by Dr. Armando Oliva and concluded that the doses of 40 mg and less were safe while the higher incidence of chest pain for the 80 mg dose precluded approval.

Summary of safety

There were 48 clinical studies in the NDA. Three long term safety studies were ongoing at the time of the NDA (108, 316 and 317) with a cut off date of 4/30/98. In these studies, over 5,000 patients received at least one dose of eletriptan for the treatment of a migraine. An additional 1,054 patients received only placebo. In two of the long term studies, 1170 patients were assigned to received physician determined treatments for migraine, mostly sumatriptan, during the open label extension. The long term studies evaluate the safety of the chronic intermittent exposure. The number of patients treating 2 or more headaches per month on average for 6 and 12 months are in the following table.

Number of patients treating on average 2 or more headaches per month		
	6 months	12 months
Eletriptan 40 mg	212	96
Eletriptan 80 mg	272	108

Deaths: There were 5 deaths reported. One patient died from a hemorrhagic cerebral infarction. It was not clear if the 45 year old female patient had taken 40 mg tablet dispensed 12 days earlier. One patient died in an automobile accident three days after taking eletriptan. Two patients committed suicide. Both of these patients had a history of depression. One of these two patients had taken 5 doses of 20 mg over a 10 week period. The other patient's deaths occurred 54 days after the last dose. One patient died with pancreatic cancer.

Serious adverse events: A 54 year old female developed chest tightness soon after receiving a 50 microgram/kg iv dose of eletriptan. This was associated with 60 to 70% constriction of right proximal coronary artery. ECG showed no changes and the vasospasm resolved within 30 minutes. The chest tightness did not resolve with resolution of the vasospasm or use of nitrates. The sponsor concluded that the chest tightness and vasospasm wither not related to each other and the vasospasm was related to catheter tip irritation.

A 50 year old female took 4 doses of 80 mg of eletriptan over a 23 day period. She was found to have a ALT of 304 (ULN 23) which resolved after 2 weeks. There were no other causes found for the ALT elevation. There were three other cases of ALT elevations which are described in the lab section.

There were 2 cases of angina, 2 cases of chest pain and a myocardial infarction reported as serious adverse events. One of the cases of angina occurred in a patient treated with sumatriptan. The other cases were in patients on eletriptan. The MI occurred 7 weeks after the last dose of treatment in a patient with underlying coronary artery disease.

Discontinuations for adverse events: 2.2% of patients on eletriptan discontinued for adverse events compared to 1.1 and 1.7% for placebo and sumatriptan, respectively. The incidence for drop outs for adverse events from the long term study only should be provided. The most common adverse events leading to discontinuation (0.3 to 0.4%) is

nausea, dizziness, asthenia and chest pain. 11 patients were discontinued for elevation of LFTs. 8 of the 11 were on eletriptan.

Adverse events: Adverse events were similar to other triptans with tightness (including chest pain), paresthesia, dyspepsia and asthenia. Many of these symptoms appeared to be dose related. The following table from Dr. Oliva's review has the more common adverse events attributed to the first attack for the single and multiple dose studies. The assessment of adverse events by race, age and sex was difficult since only a few patients were > 65, most patients were female, and 95% were white.

Table 60: (RA) Most Common AE's Attributed to 1st Dose ($\geq 2\%$)

AE	20mg	40mg	80mg	PBO
ASTHENIA	3.7	3.9	10.5	1.4
NAUSEA	3.5	3.9	6.9	2.2
SOMNOLENCE	2.3	4.4	6.6	2.1
DIZZINESS	3.0	4.4	6.3	1.7
PARESTHESIA	3.2	2.6	4.1	1.3
CHEST PAIN	0.5	1.9	3.9	0.7
HEADACHE	2.3	2.5	3.7	1.5
DRY MOUTH	1.4	2.7	3.4	1.2
VASODILATATION	1.6	1.8	3.1	1.0
HYPERTONIA	0.9	0.8	2.6	0.3
DYSPHAGIA	0.7	1.6	2.6	0.2
ABDOMINAL PAIN	0.7	1.5	2.2	0.2
SWEATING	0.2	1.0	2.0	0.5
VOMITING	0.9	1.0	2.0	2.0

Labs: There were 11 patients discontinued for elevated LFTs. 8 were on eletriptan. One patient was diagnosed as having hepatitis. This was a 54 year old female who treated 19 attacks with 32 doses of 80 mg. She had an elevation of ALT to 194 and total bilirubin to 209 (ULN 21). The patient was diagnosed with hepatitis A though the serology tests were not included in the CRF.

There were 4 cases of elevated LFTs > 3 times the ULN without other causes or elevations at baseline. All patients had taken multiple doses of 80 mg prior to the elevated LFTs. The elevations were not associated with symptoms or elevations of bilirubin. The maximum elevation was about 14 times the ULN.

Vital signs: Vital signs were not checked at the time of treatment in the outpatient studies. BP and pulse were assessed in the clinic in phase 1 study. In this study, eletriptan was associated with a small, transient increase in BP. Statistically significant increases in diastolic BP were seen at oral doses of 60 mg or greater while increases in systolic BP were seen at doses of 80 mg or higher. In general, the mean maximum change were between 10 and 15 mmHg. In a PK study evaluating subjects with hepatic failure, one subject on 80 mg developed severe hypertension. The BP increase was noted 1 hour after dosing and resolved 5 hours after dosing.

ECG: In the outpatient studies, ECGs were evaluated hours to weeks following treatment. In clinical pharmacology studies, no patients had an elevation of the QTc > 500 msec. Three subjects had an increase of > 60 msec from baseline at 1, 4 and 8 hours post dose, respectively. The increases ranged from 62 to 76 msec. In study 001, 48 volunteers were had Holter monitoring after receiving doses of 20 to 120 mg. There were no changes suggestive of ischemia.

Angiography: In study 211, a single dose of 50 micrograms/kg was given iv. The Cmax was similar to a 40 mg dose. A slight decrease in coronary artery diameter (-6%) was seen. There were no changes in pulse, BP or ECGs during the study. A single patient developed 60 to 70% reduction in the coronary artery diameter in conjunction with chest pain. The sponsor attributed the spasm to catheter tip irritation.

Adolescents: A single study evaluated 274 patients treated with 40 mg of eletriptan. Adverse events were similar to those reported in the adult studies with somnolence, dizziness, asthenia, nausea, abdominal pain, dry mouth, tightness and chest pain. No serious adverse events were reported. One patient treated with placebo followed by 40 mg discontinued because of an increase in their migraine.

Long term safety: The number of patients treating 2 or more headaches per month on average for 6 month and 1 year are in the following table.

	Freq	Treated	Visit at 6 months	Visit at 12 months
Eletriptan 40 mg	All attacks	390	309	133
	≥2 /month	262	212	96
Eletriptan 80 mg	All attacks	486	352	122
	≥2 /month	357	272	108
POT	All attacks	278	141	61
	≥2 /month	148	87	43
Blinded Therapy	All attacks	411	184	67
	≥2 /month	249	98	40

4 month safety update: The cut off date for serious adverse events was 7/17/98 in the original NDA and 10/31/98 in the update. New serious adverse events included retinal degeneration after taking a 5 doses of 40 mg.

Comments:

Many studies were included in the NDA. While over 5000 patients were exposed to a single dose of the drug, relatively few were evaluated who had chronic, intermittent exposure. Less than 300 patients have treated 2 or more headaches on average over 6 months with either 40 or 80 mg. At a minimum, we have asked for sponsors to follow ICH recommendations for 300 to 600 patients treating headaches over 6 months. We have asked for the exposure to be at least 2 headaches per month, on average. The low exposure limits our assessment of the safety of the 40 or 80 mg dose. We have observed adverse events at 80 mg not seen at 40 mg but this may be related to relatively low numbers exposed to 40 mg chronically. We may be able to gain additional information

from studies that were ongoing at the time of the NDA. The sponsor has close to 100 and 40 patients in a third study which was blinded at the time of submission.

There were 5 deaths in the database. Two patients with depression committed suicide. The relationship to drug is unlikely with one of these suicides coming 54 days after the last dose. One patient died with a hemorrhagic stroke but it is not clear if and when the patient even took the study treatment.

The evidence for the potential for this drug to cause cardiac vasospasm is similar to that seen with other drugs. Angiographic evidence for vessel constriction was similar to that seen with sumatriptan. The single case of a patient with vasospasm and chest pain associated with receiving an iv dose of eletriptan strongly suggests a potential of this drug to cause vasospasm. This may be a dose related phenomenon with a higher incidence of chest pain in patients receiving 80 mg compared to 40 mg or even compared to patients dosed with sumatriptan.

Another potential dose related adverse event is an elevation of LFTs. 4 patients exposed to eletriptan long term developed elevation of LFTs > 3 times the ULN. These elevations occurred in patients on 80 mg. The elevations were reversible and patients did not have symptoms of liver toxicity. A single patient developed hepatitis with elevation of bilirubin. While this patient was reported to have hepatitis A viral infection, the lab tests verifying this diagnosis were not included in the study report. In review of the Maxalt database, Dr. Oliva noted that an elevation of ALT was seen.

Elevation of BP, as seen with other triptans, was reported with eletriptan. One patient with liver failure had a clinically significant elevation after receiving a single dose of 80 mg.

Other adverse events were similar to those seen with other triptans.

In general, eletriptan appears to have a safety profiles similar to other triptans. An exception may be liver toxicity. The more serious adverse events may be dose related increasing with doses of 80 mg. Potentially serious adverse events include coronary artery vasospasm, elevation of BP, liver toxicity. The experience with chronic intermittent doses of 40 and 80 mg is limited.

Conclusions

Eletriptan is an effective acute treatment for migraines with a safety profile similar to other 5HT₁ agonists. It does not appear to offer any advantages over approved 5HT₁ agonists. Comparative trials with sumatriptan did not demonstrate a clear superiority in the risk to benefit ratio.

The sponsor conducted an extensive evaluation of the efficacy of the drug. They did not do the same for the safety evaluation. The doses in the animal toxicology studies were

low, the exposure to chronic dosing was under the 300 to 600 needed and the evaluation for the CYP3A4 interaction was minimal.

Recommendations

I recommend that additional information be obtained prior to approval.

The sponsor should conduct additional studies to evaluate the extent of the interaction with inhibitors of CYP3A4. At this time, there is insufficient information to determine what effects inhibitors will have on the C_{max} and AUC of the drug. Without this information, labeling would need to contraindicate the use of all CYP3A4 inhibitors with eletriptan. The effectiveness of such a contraindication in preventing the concomitant use of drugs is questionable. It would be better if we had more information on these potential interactions prior to approval.

The drug is an effective acute treatment for migraines. The application provides evidence that doses of 20, 40 and 80 mg are effective for the acute treatment of migraines. There is some clinical evidence to suggest that doses of 40 and 80 mg are more effective than 20 mg. As Dr. Oliva points out, doses of 10 mg may also be effective. While there is no statistical evidence and little clinical evidence to suggest that 80 mg is significantly more effective than 40 mg, there is evidence to suggest that adverse events including serious ones, may be more frequent with 80 mg. I agree with Dr. Oliva that the 20 and 40 mg doses should be the recommended doses.

A reservations for use of the 80 mg dose of the drug is based on the size and findings of the safety database. The safety data suggests that the safety profile of the 20 and 40 mg dose is similar to sumatriptan while the 80 mg may have a higher incidence of safety problems and some additional issues as well such as elevation of LFTs. In addition, the animal chronic toxicity studies were conducted at doses that do not provide significantly higher levels of exposure than those seen in humans treated with 80 mg x 2.

The sponsor needs to provide additional chronic safety data. For all recently approved migraine drugs, we have asked for safety data from only 300 to 600 patients treating at least two migraines, on average, for 6 months. While the sponsor has this amount of data for the combined doses of 40 and 80 mg, we should also have this amount of data from the 40 mg dose alone since there was some evidence for specific toxicity at the 80 mg dose (elevated LFTs) which may also occur with the 40 mg dose. The sponsor should have this data in studies that were being conducted at the time of the submission of the NDA. When evaluating this data, the sponsor should pay particular attention to serious adverse events including evidence for cardiac events, BP changes, and liver toxicity.

In regards to the preclinical studies, the doses used in the fertility studies were too low to adequately determine the effect of the drug on fertility. Fertility studies are very important for migraine treatments since the majority of patients are women of childbearing potential. Dr. Fitzgerald feels that this study should be initiated as soon as possible but can be completed following approval with appropriate labeling. Since there

are other issues to resolve prior to approval, the sponsor does not need to wait until after approval to conduct these studies. This study can and should be completed prior to the time of approval allowing us to provide complete and accurate labeling. In addition, the results from studies evaluating the peri and post natal learning and memory should be provided. As with the fertility study, evaluation of the effects of the drug on learning and memory of the newborn is important for migraine treatments because of population being treated. Based on previous communications, this study was we started in March and should be completed at this time.

Labeling recommendations

Draft Labeling

1 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

Executive CAC
June 15, 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Ken Hastings, Ph.D., HFD-590, Alternate Member
Glenna Fitzgerald, Ph.D., HFD-120, Team Leader
Robin Huff, Ph.D. and Barry Rosloff, Ph.D., Presenting Reviewers

Author of Draft: Robin Huff, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA: 21,016

Drug Name: Eletriptan (Relpax™)

Sponsor: Pfizer

Mouse Carcinogenicity Study:

In the 2 year mouse study, doses of 20, 90 and 400 mg/kg/day were administered in the diet. The high-dose produced deficits in weight gain such that terminal body weights were 5 and 13% less than control in high-dose males and females, respectively. Although food consumption was also decreased, the onset relative to body weight effects was such that palatability did not appear to be a problem. The incidence of liver adenoma was statistically significantly increased in high-dose males, 12/50 v. 2/50 and 7/50 in control groups. The increase was due to an increase in eosinophilic, but not basophilic tumors. There was no increase in carcinomas. Other pathology in the liver included foci of alteration, single cell necrosis, pigmentation, hepatocyte hypertrophy, karyomegaly, and heterogeneous cytoplasm. The other tumor type that showed an increased incidence at the high-dose was Harderian gland adenoma. The incidences were 0, 6, 6, 6, and 12% in control-1, control-2, low-dose, mid-dose and high-dose males, respectively, and 0, 0, 6, 4, and 6% in control-1, control-2, low-dose, mid-dose and high-dose females, respectively. The incidence of hypersecretion was increased in high dose males, 70% v. 42% in controls, but the incidence of hyperplasia was not increased. Harderian gland adenoma is a common tumor type, and incidences were within historical control ranges reported in the literature and were not statistically significant in comparisons to both individual control groups. Based on toxicokinetic data collected in the dose range-finding study, the AUC achieved at the high dose was approximately 7-fold the 3000 ng.h/ml AUC achieved in humans given the maximum recommended daily dose of two 80 mg tablets.

Rat Carcinogenicity Study:

In the 2 year rat study, doses of 3, 15 and 75/50 mg/kg/day were administered in the diet. The 75 mg/kg dose was reduced to 50 mg/kg in females after 8 months due to an excessive decrease in body weight gain. Body weight gain was decreased at the high-dose, such that terminal body weights were 20 and 30% less than control for males and females, respectively. The decrease in BW gain may be responsible for the decreased mortality observed in high-dose males. Although

food consumption was also decreased, the onset relative to body weight effects was such that palatability did not appear to be a problem. The incidence of testicular interstitial cell adenoma was increased at the high dose, 11/64 v. 4/65 and 3/65 in control groups. The sponsor ascribed the increase to the increased longevity of high-dose males, but the statistical reviewer, Roswitha Kelly, contends that the finding is significant even after correction for survival. The only other tumor incidence that was notably increased was that of histiocytic sarcomas in the lymphoreticular system of mid-dose males, 4/65 v. 1/65 and 1/65 in control groups. Although a similar increase did not occur at the high dose, the excessive decrease in body weight gain at the high dose may have decreased tumor expression. The incidence at the high dose did not exceed the historical control range reported in the literature. Based on extrapolations from toxicokinetic data collected in the dose range-finding study which used doses of 100, 200 and 300 mg/kg, the AUC's attained at the mid- and high-doses were approximately equal to and approximately 2 times, respectively, the 3000 ng.h/ml AUC achieved in humans given the maximum recommended daily dose of two 80 mg tablets. Evidence from gavage studies suggests that higher doses and exposures could have been achieved by gavage rather than dietary administration. A 100 mg/kg dose caused minimal toxicity and no deficit in body weight gain when administered for 1 month. Based on toxicokinetic data collected for 15 and 50 mg/kg doses, the AUC for male and female rats at the 100 mg/kg dose is predicted to be 3 and 6-fold the 3000 ng.h/ml AUC achieved in humans at the maximum recommended daily dose of two 80 mg tablets.

Executive CAC Recommendations and Conclusions:

1. Doses were adequate in the mouse study based on decrements in body weight gain.
2. The increase in liver adenomas should be included in labeling, with the caveat that this tumor type is common in mice. The Harderian gland adenomas should not be included in labeling.
3. Doses were adequate in the rat study based on decrements in body weight gain. Dietary administration is acceptable, even though it appears that higher exposures might have been attainable with gavage administration, because palatability does not appear to have factored into the reduced body weight gain that defined the MTD.
4. The increase in testicular adenomas and histiocytic sarcomas should be included in labeling only if the incidences exceed historical control. (Note added after meeting: The 17.2% incidence of testicular interstitial cell adenoma at the high-dose notably exceeds the 1.4 – 10.0% historical control range [mean 4.7%] reported by ———. As noted above, the 6.2% increase in histiocytic sarcoma does not exceed the 1.4 – 7.1% historical control range [mean 1.6%] reported by ———)

/S/
Joseph DeGeorge, Ph.D.
Chair, Executive CAC

6/21/99
cc:\n
/Division File, HFD-120
/GFitzgerald, HFD-120
/RHuff, HFD-120
/ASeifried, HFD-024

**CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT
AND
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET**

P/T REVIEWER(s): Robin Huff (rat study)
Barry Rosloff (mouse study)

MEETING DATE: June 15, 1999

IND/NDA: NDA 21-016
DRUG CODE#: UK-116,044
DIVISION(s): HFD-120
DRUG NAME(s): Eletriptan (Relpax™)

SPONSOR: Pfizer

LABORATORY: Pfizer, Centre de Recherche, Amboise, France

CARCINOGENICITY STUDY REPORT DATES: 9/98 (rat), 6/98 (mouse)

THERAPEUTIC CATEGORY: migraine

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: 5HT_{1B/D} agonist

MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay):

Equivocal in the human lymphocyte chromosomal aberration test. In the first trial, under -S9 conditions the percent of cells with aberrations exceeded control at all doses (6.5, 6.5, 3.0 and 6.0% v. 2.5%), but the increases were not statistically significant or dose-related. Under +S9 conditions, the percent of cells with aberrations was statistically significantly increased at the two highest concentrations tested (3.5 and 4.0% v. 0.5%, historical control 0 - 3%). In the second trial, results were negative under both - and +S9 conditions.

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RAT CARCINOGENICITY STUDY

RAT STUDY DURATION (weeks): 104

STUDY STARTING DATE: 1994

STUDY ENDING DATE: 1996

RAT STRAIN: Sprague-Dawley

ROUTE: diet

DOSING COMMENTS: HD in females was reduced from 75 to 50 mg/kg after 8 months because of excessive decrease in BW gain.

NUMBER OF RATS:

- Control-1 (C1): 65
- Control-2 (C2): 65
- Low Dose (LD): 65
- Middle Dose (MD): 65
- High Dose-1 (HD): 65

RAT DOSE LEVELS (mg/kg/day):

- Low Dose: 3
- Middle Dose: 15
- High Dose: 75 (reduced to 50 in females after 8 months)

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible):
MTD (decreased weight gain)

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): Not sought

RAT CARCINOGENICITY (conclusion: negative; positive; MF; M; F):
Positive (high dose males, ?mid-dose males)

RAT TUMOR FINDINGS (details):

Tumor	Incidence (63 – 65 tissues/gr examined)							
	Control ^a		LD		MD		HD	
	M	F	M	F	M	F	M	F
Testes interstitial adenoma	4	na	1	na	3	na	11	na
Lymphoreticular System histiocytic sarcoma	1	0	0	0	4	1	2	1

^aThe greater of the two control group incidences is provided.

RAT STUDY COMMENTS: Testicular interstitial cell adenomas should go in labeling.

MOUSE CARCINOGENICITY STUDY

MOUSE STUDY DURATION (weeks): 104

STUDY STARTING DATE: 1994

STUDY ENDING DATE: 1996

MOUSE STRAIN: CD-1

ROUTE: diet

DOSING COMMENTS: none

NUMBER OF MICE:

- Control-1 (C1): 50
- Control-2 (C2): 50
- Low Dose (LD): 50
- Middle Dose (MD): 50
- High Dose (HD): 50

MOUSE DOSE LEVELS (mg/kg/day):

- Low Dose: 20
- Middle Dose: 90
- High Dose: 400

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible):

1. MTD (decreased weight gain)
2. AUC (sponsor claims 33x AUC but we calculate 7x)

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): Not sought

MOUSE CARCINOGENICITY (conclusion: negative; positive; MF; M; F):

Positive (high dose males)

MOUSE TUMOR FINDINGS (details):

1. Hepatocellular adenomas in HD M (total adenomas 24% vs 9% in controls; eosinophilic adenomas only: 14% vs 0% in controls). Foci of cellular alteration also increased in HD M.
2. Equivocal increase in Harderian gland adenomas in HD M (12% vs 3% in controls). Harderian gland hypersecretion, but not hyperplasia, increased in HD M.

MOUSE STUDY COMMENTS: Hepatocellular adenomas should go in labeling.

I. Rat 2-Year Carcinogenicity Study (94-912-03), GLP, QA
Pfizer Central Research (Groton, CT), conducted in 1994 – 1996

Sprague-Dawley rats – 3, 15, 75 mg/kg in diet (lowered to 50 mg/kg for F after 8 months)
65/s/gr with 2 control groups (batch R109 and R203)

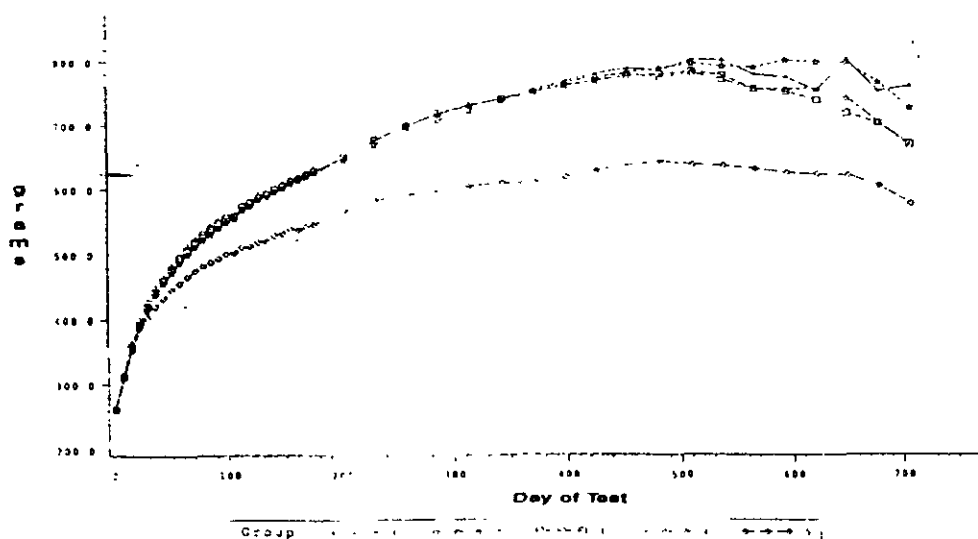
Mortality There was no detrimental effect of treatment on survival throughout the study. In fact, survival in HD M exceeded that of controls from approximately 17 months onward. Survival at the end of the study is tabulated below.

Sex	Number of Animals Alive at Study Termination				
	C1	C2	LD	MD	HD
Male	17	22	23	19	42
Female	25	20	20	22	27

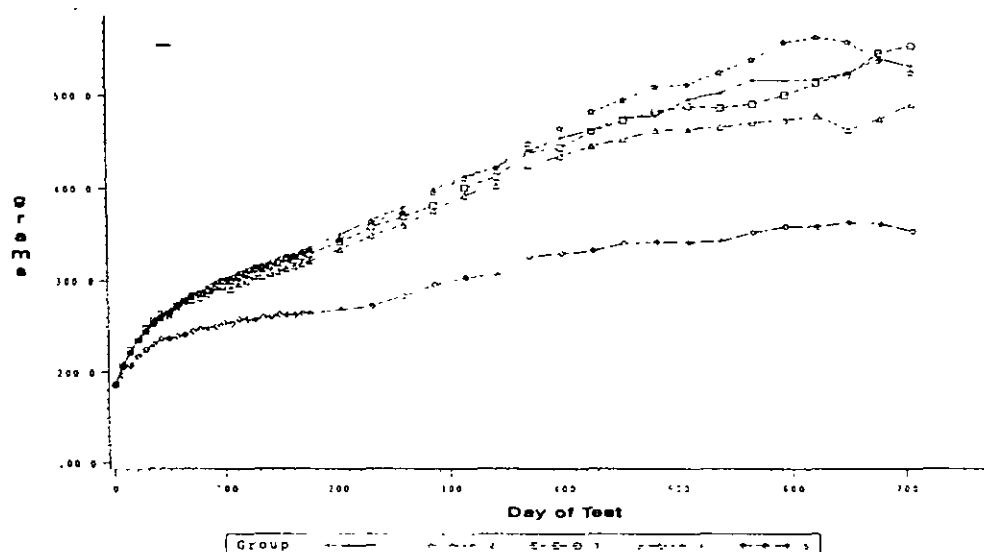
Clinical Signs There were no notable clinical signs.

Body Weight BW gain was reduced throughout the study in HD M and F such that BW's at the end of the study were 20 and 33% less than control, respectively (sponsor-supplied BW curves are provided below). Because of the excessive decrease in BW gain, the sponsor decreased the HD for F from 75 to 50 mg/kg after 8 months of treatment. From 17 months onward BW in MD F was 6 – 12% less than control, with differences being occasionally statistically significant. Effects on BW were generally paralleled by decreased food consumption, although the decreased BW gain in HD F was evident within the first weeks of the study, preceding the effect on food consumption. The decrease in food consumption does not appear to be related to palatability because it was not notable until weeks 6 – 8.

Males



Females



- Hematology** Parameters were measured at 6, 12 and 18 months in 10/s/gr. There were no notable findings.
- Clinical Chem** Parameters were measured at 6, 12 and 18 months in 10/s/gr. Bilirubin was increased 58 – 75% and 23 - 53% in all treated M and F groups respectively, but only at 6 months. Triglycerides were decreased ~60% in HD F at 12 and 18 months. A similar decrease did not reach statistical significance in HD M at 18 months, but appears to be a drug-related effect based on individual animal data.
- Toxicokinetics** Plasma concentrations of eletriptan were determined on Days 91 and 177 in 5/s/gr. Concentrations in the LD group were generally at or below the 4 ng/ml level of detection. Concentrations in the MD group were 41 and 49 ng/ml on Days 91 and 177, respectively, and in the HD group were 290 and 430 ng/ml, respectively.
- Organ Weights** Absolute kidney weight was 20% less than control in HD M and absolute liver weight was 21% less than control in HD F. Relative brain and testis weights were 24 and 53% greater than control, respectively, in HD M. Relative heart, kidney and brain weights were 17, 25 and 40% greater than control, respectively, in HD F. The effect on organ weights likely reflects the decreased BW gain at the HD.
- Pathology** The sponsor reports no treatment-related gross pathology (no data were provided). Notable histopathology changes are tabulated below and include an increased incidence of testicular interstitial cell adenoma in HD M. The sponsor states that the increased incidence was not significant after Bonferoni

correction for multiplicity of testing, but Bonferoni correction in carcinogenicity studies is not accepted by the Agency because of its tendency to overcorrect given the sheer number of comparisons being made. The sponsor also attributes the increased incidence to the greater longevity of the HD M group (all testicular tumors were identified in animals surviving ≥ 19 months); however, the increase is statistically significant even after adjustment for survival. The incidence of histiocytic sarcomas was increased in MD M, but did not exceed the historical control range reported by _____ for studies conducted in 1984 – 1989.

Increased non-neoplastic histopathology was limited to HD M and included an increased incidence of liver eosinophilic foci, thyroid follicular cell hyperplasia, and pituitary pars distalis hyperplasia. The incidence of several histopathological findings were decreased in HD M and/or F, likely owing to the deficit in BW gain experienced at the HD.

	Incidence (63 – 65 tissues/gr examined)							
	Control ^a		LD		MD		HD	
	M	F	M	F	M	F	M	F
Neoplastic Findings								
Testes interstitial adenoma	4	na	1	na	3	na	11	na
Lymphoreticular System histiocytic sarcoma	1	0	0	0	4	1	2	1
Non-neoplastic Findings								
Liver, eosinophilic foci	8	9	6	7	5	5	25	8
periportal vacuolation	8	10	9	12	2	7	1	1
Thyroid, follicular cell hyperplasia	5	2	6	2	8	1	15	1
Pituitary, <i>pars distalis</i> hyperplasia	7	9	5	4	3	2	14	6
Adrenal, cortical vacuolation	15	5	20	4	14	3	6	4
Kidney, chronic nephropathy	49	24	53	14	52	20	37	6
Mammary Gland, fibroadenoma	0	19	0	11	0	15	0	5
Testes, periarteritis	14	na	19	na	15	na	5	na
tubular atrophy	16	na	21	na	15	na	8	na

^aOf the two control groups the one that was the least different from the treated group was selected for inclusion in the table.

Summary

The incidence of testicular interstitial adenoma was increased in HD M (11/64 v. 4/65). The sponsor attributed the increase to the greater longevity of HD M compared to control; however, the increase is statistically significant even after adjustment for survival. The only other tumor incidence that was notably increased was that of histiocytic sarcomas in the lymphoreticular system of MD M (4/65 v. 1/65). Although a similar increase did not occur at the HD, the excessive decrease in BW gain at the HD (BW 20% less than control at study

termination) may have decreased tumor expression at the HD. The 4/65 incidence of histiocytic sarcoma at the MD did not exceed the control incidence reported by _____ for studies conducted in 1984 – 1989 (data closer to the time frame of this study are not available).

Non-neoplastic changes observed in HD M included increased incidences of eosinophilic foci in the liver, follicular cell hyperplasia in the thyroid and *pars distalis* hyperplasia in the pituitary. There were also a few changes indicative of improved general health in HD M and F, likely related to the decreased BW gain observed at the HD. The incidences of hepatic periportal vacuolation, adrenal cortical vacuolation, chronic nephropathy, testicular periarteritis, testicular tubular atrophy, and mammary gland fibroadenoma were decreased in HD M and/or F.

The excessive decrease in BW gain at the HD may have compromised tumor expression, making the MD of 15 mg/kg the highest dose from which tumor data can be reliably evaluated. On a mg/m² basis this dose is approximately equal to the maximum recommended daily clinical dose. The plasma levels achieved at this dose were approximately 20% of the C_{max} achieved in humans. No AUC estimations were made in this study; however, extrapolating linearly from results in the dose range-finding study (100, 200, 300 mg/kg), the AUC achieved at 15 mg/kg was approximately equal to the 3000 ng.h/ml exposure achieved in humans at the maximum recommended daily dose. It appears that significantly higher doses could have been achieved by gavage rather than dietary administration. In a one month gavage study in which the HD was 100 mg/kg, there was no effect on BW and toxicity was limited to increased liver weight (~20%) and thyroid follicular hypertrophy in F only. Furthermore, essentially no toxicity was observed in a 6 month study at the HD of 50 mg/kg.

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ON ORIGINAL

II. Mouse 2-Year Carcinogenicity Study (94021), GLP, QA

This study was reviewed by Barry Rosloff, Ph.D.

A) DOSAGE

50/sex at 0, 0, 20, 90, or 400 mg/kg/day, in diet

Strain: CD-1

Drug batch numbers: R107 and R109

Lab performing study: Pfizer
Centre de Recherche
37401 Amboise Cedex
France

Dates of study: 1994-1996

B) RESULTS

1) Observed signs.

No drug effects.

2) Mortality

Results shown in attached figures.

The sponsor concludes that mortality was decreased in MD and HD F. (Overall survival = 44%, 58% and 68% in control F, MD F, and HD F, resp.) However, as indicated in the attached figure, mortality in all M groups, although similar to controls at the end of the study, was less than that in controls during most of the 2nd year (not dose-related).

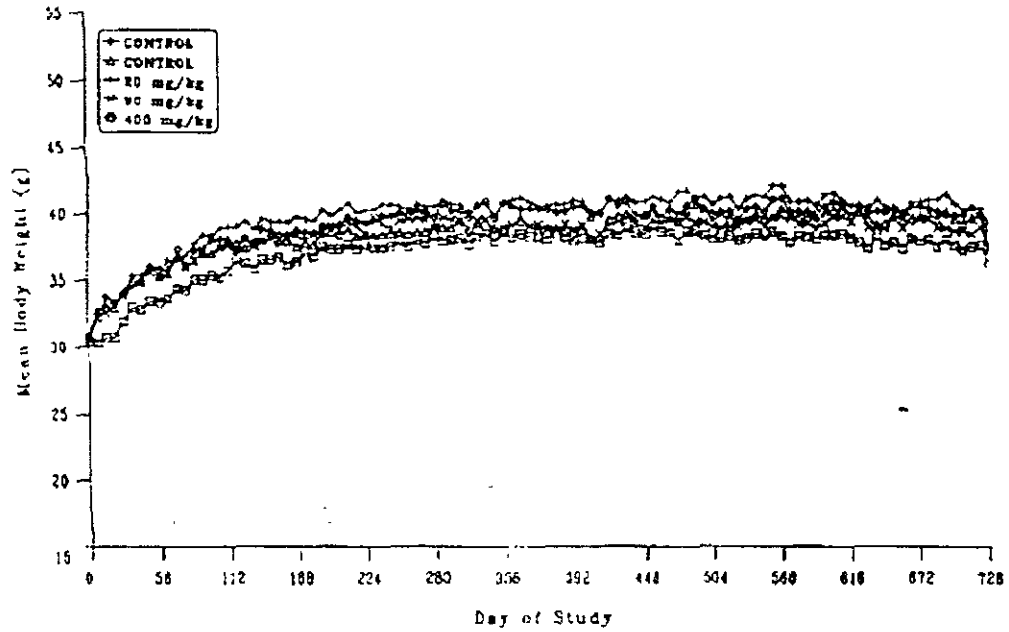
3) Bodyweight

Weight gain was slightly decreased in HD M and HD F starting from the first week of treatment. Weights near the end of the study were approximately 5% and 13% below control in HD M and HD F, resp. Weight gain was slightly decreased in MD F beginning after the 2nd month treatment, although this only occasionally reached statistical significance; weights near the end of the study were

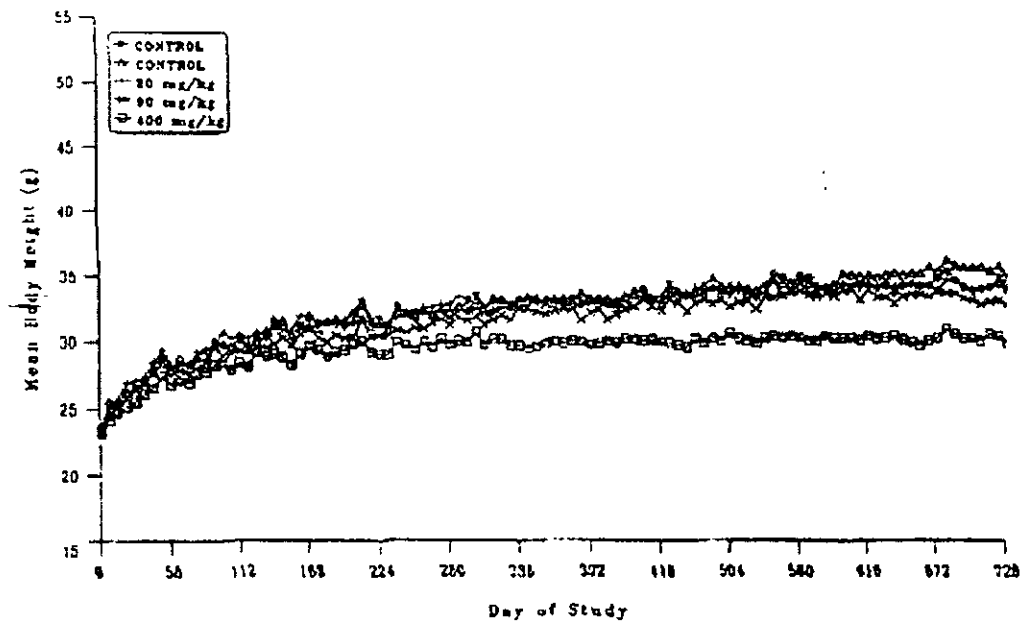
approximately 5% below control. Weight gain in LD M was very slightly increased after 3 months.

Sponsor-supplied bodyweight curves below.

Males



Females



4) Food Consumption

Slightly decreased at HD of both sexes throughout the study, with the notable exception that consumption was slightly (and statistically significantly) increased in HD F during week 1. As with weight gain, food consumption was slightly decreased in MD F, although this did not become apparent until later in the study (approx. 8 months) than did the decrease in weight gain. Food consumption was sporadically slightly increased in LD M.

Food consumption curves are attached.

5) Water Consumption

At HD, slight decreases throughout most of study (although slightly increased first week). Slight decreases in MD F during latter part of study.

6) Ophthalmoscopic exam

(Done in 25/sex in controls and HD pre-study; repeated every 6 months in survivors among these animals)

No drug effects.

7) Hematology

(Done at termination)

Slightly decreased RBC, Hb, and Hct, and slightly increased platelets, in HD M. Very slight, non-statistically significant changes in same directions as above seen in MD M.

Other parameters measured: RDW, large unstained cells, WBC, differential, bone marrow smears. (No summary data shown for the latter).

8) Blood chemistry

(Done at termination)

- a) ALT, AST, and AP increased in HD M. Mean values approx. 2x control; highest individual value at HD approx. 2.3x, 3x, and 1.3x highest concurrent control for ALT, AST, and AP, respectively.

- b) Glucose decreased in MD and HD M (D-R) and HD F; mean value at HD approximately 80% of control.
- c) Na very slightly increased in HD M. (Mean value approximately 2 mmol/L above control).
- d) Cl moderately increased at MD and greatly increased at HD, said to be due to interference with the assay by the bromide moiety of the drug.
- e) Other parameters measured: K, Ca, urea, cholesterol, triglycerides, protein albumin

9) Urinalysis not performed

10) Organ weights

Absolute and relative liver weights increased in MD and HD M. Relative weights were approximately 1.5 and 1.13x control at MD and HD, resp. Relative liver weight was slightly increased in HD F (1.1x control) with no effect on absolute weight.

11) Gross pathology

Text states no effect; no summary table presented.

12) Histopathology

(Organs shown in the list below, plus organs with macroscopic abnormalities, were examined in all groups. Summary tables did not break down results by animals which survived to termination and those which did not. These tables are attached [separate tables for neoplastic and non-neoplastic findings].)

Adrenal glands
Aorta
Brain
Cervical lymph node
Colon
Duodenum
Epididymides
Eyes/Hardarian glands
Gall bladder
Heart
Ileum
Kidneys
Liver
Lung
Mammary gland/skin
Mesenteric lymph node
Oesophagus
Ovaries

Pancreas
Parathyroid
Pituitary gland
Prostate
Salivary glands
Sciatic nerve
Spleen
Sternum with marrow
Stomach
Striated muscle
Testes
Thymus
Thyroid gland
Trachea
Urinary bladder
Uterus
Vagina

a) Liver

The following showed increased incidence in HD M: hepatocellular adenoma, foci of cellular alteration, single cell necrosis, pigmentation (mainly lipofuscin in Kupffer cells), and various "centrilobular changes" (hepatocyte hypertrophy, karyomegaly, heterogeneous cytoplasm). Centrilobular changes also seen in 2/50 MD M and 2/50 HD F. (Incidence values shown in sponsor's summary tables; some also shown in the excerpt below taken from the "Results" section which also contains additional descriptions of some the lesions). Note that eosinophilic, but not basophilic adenomas were increased; also note that according to the sponsor's descriptions some other drug-related findings were also eosinophilic in nature. The incidence of liver carcinomas was not increased.

Liver

Findings in the liver were generally limited to the high-dose males and consisted of an increased incidence of a spectrum of centrilobular findings, foci of cellular alteration and eosinophilic adenomas, all of which correlated with the increased organ weight.

The centrilobular microscopical findings usually occurred together and consisted of:

- Hepatocellular changes characterized by enlargement of hepatocytes which displayed variably enlarged nuclei (karyomegaly) and heterogeneous cytoplasm containing deep eosinophilic to amphophilic scattered small irregular aggregates within a light eosinophilic background. Hepatocellular changes were minimal (involving a few centrilobular hepatocytes) to severe (diffuse). The hepatocellular changes also occurred in 2/50 mid-dose males and 2/50 high-dose females.
- Single cell necrosis characterized by scattered necrotic hepatocytes.
- Pigmentation consisting mainly of lipofuscin within the cytoplasm of Kupffer cells.

Mixed foci of cellular alteration were recorded only in the high-dose male group. They were composed of enlarged hepatocytes with nuclear and cytoplasmic characteristics similar to those described above for the centrilobular hepatocellular changes. There was also a slight increase in the incidence of basophilic foci.

The incidence of hepatocellular adenomas was slightly increased owing to the presence, within the high-dose male group, of 7 adenomas of the eosinophilic type made up of enlarged eosinophilic hepatocytes. The incidence of both basophilic adenomas and hepatocellular carcinomas was similar to controls.

In addition, the incidence of spongiosis hepatitis was slightly increased in the high-dose female group (5/50 vs 1/50 in control female groups). In the absence of any associated compound-induced hepatic changes, this variation was considered to be of no toxicological importance.

Relevant hepatic findings in males

	<u>Controls 1</u> (n=50)	<u>Controls 2</u> (n=50)	<u>20 mg/kg</u> (n=50)	<u>90 mg/kg</u> (n=50)	<u>400 mg/kg</u> (n=50)
Centrilobular findings:					
Centrilobular hepatic changes				2	22 ***
Single cell necrosis	7	5	7	8	24 ***
Pigmentation		2		3	21 ***
Foci of cellular alteration:					
Basophilic foci		2	1	2	5 **
Mixed foci					10 ***
Neoplasms:					
Adenoma *	2	7	2	3	12 **
Basophilic	2	7	2	3	5
Eosinophilic					7
Carcinoma	3	2	4	4	4

, * = statistically significant at p=0.01, p=0.001

* Adenoma was analyzed statistically as a whole only

Note that some non-neoplastic findings in liver were decreased in some drug groups, e.g. "necrosis" in males, and extramedullary hemotopoeisis, pigmentation, and basophilic foci in females.

b) Harderian gland

The incidence of adenoma was increased in HD M (12% vs 3%, 6% and 6% in controls, LD and MD, resp.). The incidence of hypersecretion in Harderian gland was also increased in HD M (70 % vs 42 % in control). The incidence of hyperplasia was not increased.

Although apparently not considered drug-related by the sponsor, the incidence of harderian gland adenoma in females was 0%, 6%, 4% and 6% in controls, LD, MD, and HD, resp. The incidences of hypersecretion and hyperplasia were not increased in females.

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SUMMARY

A 2 year dietary carcinogenicity study was performed in CD-1 mice at daily doses of 20, 90, and 400 mg/kg. There were no drug-related signs or effects on ophthalmoscopic exams. Mortality was decreased in MD and HD F. Although there was no drug effect on percent survival in males at termination, mortality was lower than controls in all male groups (not D-R) during the second year of the study. Bodyweight gain and food consumption were decreased in MD and HD F and HD M; final weights were 5%, 13%, and 5% below controls, respectively. Hematology and blood chemistry exams showed (1) slightly decreased RBC, Hb, and Hct, and slightly increased platelets, in HD M and equivocally in MD M, (2) increased ALT, AST and AP in HD M, (3) decreased glucose in MD and HD M and HD F, and (4) increased chloride at MD and HD said to be due to assay interference by the drug.

Absolute and relative liver weights were increased in MD and HD M; relative (but not absolute) liver weight was slightly increased in HD F. Gross pathology exams were said to show no drug effect although no summary tables were presented. Histopathology exams showed an increase in eosinophilic hepatocellular adenomas in HD M (14% vs 0% in controls; incidence of total [eosinophilic + basophilic] adenomas = 24% vs 9% in controls). Also increased in liver of HD M were foci of cellular alteration, single cell necrosis, pigmentation of Kupffer cells, and centrilobular changes (hepatocyte hypertrophy, karyomegaly, heterogeneous cytoplasm). (Centrilobular changes also seen in 2/50 MD M and 2/50 HD F.) There were no drug effects on the incidence of hepatocellular carcinoma.

There was a slight increase in the incidence of adenoma of the harderian gland in HD M (12% vs 3% in controls). The incidence of hypersecretion in harderian gland was also increased in HD M; the incidence of hyperplasia was not. Although apparently not statistically significant by the sponsor's analysis, it is noted that the incidence of harderian gland adenomas in females was 0%, 6%, 4%, and 6% in controls, LD, MD and HD respectively. The incidence of hypersecretion and hyperplasia were not increased in females.

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EVALUATION

Although the drug did not cause any observed signs, an MTD may be considered to have been reached based on decreased weight gain; final weights at HD (400 mg/kg) were 5% and 13% below controls in M and F, respectively. (Slight decreases in weight gain were also seen at this dose in a 3 month range-finding study; higher doses were not tested). Since food consumption was decreased in the same groups in which weight gain was decreased, the possibility of poor palatability as an explanation arises. In HD M, both food consumption and bodyweights were decreased from the first week of treatment, which would support this explanation. However, in HD F, although bodyweights were decreased from the first week, food consumption showed a slight increase during the first week. Furthermore, in MD F, decreases in weight gain did not become apparent until after the second month, and decreased food consumption did not become apparent until 8 months. It thus appears likely that poor palatability is not a necessary cause of the decreased weight gain, although a role for this cannot be ruled out (especially in HD M).

Regarding the adequacy of the doses used, the sponsor also states that the AUC for parent drug at a dose of 400 mg/kg (22 ug.hr/ml, obtained in the 3 month range-finding study, results attached) is about 33 fold higher than that produced in humans "at the maximal daily clinical dose". However, note that using a maximum human dose of 80 mg b.i.d., and an estimated daily AUC of 3 ug.hr/ml (per information provided by Biopharm reviewer), a factor of 7 is calculated. It is also noted that no comparative exposure data for metabolites were presented for this highly metabolized drug.

Although hepatocellular adenoma is a common tumor type in this strain of mice, the increased incidence in HD M was clearly drug-related, particularly in view of the increase in foci of cellular alteration. The sponsor suggests that the increase in adenomas is related to hepatic enzyme induction; however, it is noted that the enzyme-inducing effect (elevated liver P-450 content) as measured in the 3 month range-finding study was thought to be small. (Also note that aside from a neoplastic effect, other liver toxicity was demonstrated in this study, including elevations of ALT, AST and AP, increased liver weight, and various histopathological changes.)

The small increases in adenomas of harderian gland are somewhat equivocal. Although statistically significant by the sponsor's analysis, the report states that a drug effect in HD M is "unlikely" since the incidence (12%) was said to be "only slightly above our historical data;" however, the only such data cited was an incidence of 5/50 in a control group "of a recent study". (In contrast, it is stated in a 1990 book [Faccini, et. al., Mouse Histopathology], that the historical incidence at Pfizer/Amboise [where the present study was performed] is under 2%. On the other hand, other published data do show higher values for CD-1 mice, e.g. 13% [range 0-18%] in males and 5% [range 0-7%] in females in a recent ——— publication). There was no strong evidence for an earlier onset of adenomas in HD M; 3 were found at termination and 1 each on days 684, 709, and 734; all 3 control tumors were found at termination. The fact that survival was greater than controls in most drug groups may have played a role in the increased tumor incidence, although the sponsor's analysis, which presumably took this into account, still

showed a statistically significant increase in HD M. In support of an effect in HD M was the finding of increased hypersecretion in this group. Increased hypersecretion was not seen in females. Increased hyperplasia was not seen in males or females.

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ON ORIGINAL

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 10/25/02

DUE DATE: 12/20/02

ODS CONSULT #: 02-0206

TO:

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
(HFD-120)

THROUGH:

Lana Chen
Project Manager
(HFD-120)

PRODUCT NAME:

Relpax

(Eletriptan Hydrobromide) Tablets,
20 mg (base), 40 mg (base), 80 mg (base)

NDA#: 21-016

NDA SPONSOR: Pfizer Inc.

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY:

In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Relpax" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS has no objections to the use of the proprietary name, Relpax. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. This is considered a tentative decision and the firm should be notified that the name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

/S/

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
- Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 20, 2002
NDA# 21-016
NAME OF DRUG: Relpax (Eletriptan Hydrobromide) Tablets,
20 mg (base), 40 mg (base), and 80 mg (base)
NDA HOLDER: Pfizer Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for an assessment of the proposed proprietary name Relpax. Draft container labels (heat sealed card), package insert, professional sample, carton, starter kit, and patient information labeling was reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Relpax is the proposed proprietary name for, Eletriptan Hydrobromide Tablets, which are indicated for acute treatment of migraine with or without aura in adults. The proposed dose of Relpax for migraine is 40 mg at the time of headache then a second dose may be taken in 2 hours if needed. The sponsor has proposed to market 20 mg, 40 mg, and 80 mg Relpax Tablets in dose cards with 6 tablets on each card.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Relpax to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-02, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each name, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Relpax. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two established names that were thought to have the potential for confusion with Relpax. This product is listed in Table 1 (below), along with the dosage forms available and usual dosage. The panel also expressed concern with the possibility of confusion between Relpax and drug products which have some phonetic version of the word "pack" in their name, e.g., Z-Pak.
2. DDMAC did not have concerns about the name with regard to promotional claims.

Table 1. Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Relpax	Eletriptan Hydrobromide Tablets, 20 mg (base), 40 mg (base), and 80 mg (base)	40 mg with a repeat dose in 2 hours if needed	
Relafen	Nabumetone Tablets USP, 500 mg or 750 mg	1500 mg to 2000 mg daily in a single dose or twice daily.	LA
Raplon***	Rapacuronium Bromide Injection, 100 mg/vial and 200 mg/vial	As directed for neuromuscular blockade	LA
Valtrex****	Valcyclovir Hydrochloride Tablets, 500 mg (base) and 1 gram (base)	Treatment: 1 gram twice or three times daily. Suppressive Therapy: 500 mg to 1 gram once a day	SA
*Frequently used, not all-inclusive. **L A (look-alike) ***Discontinued Drug Product ****Discovered after independent review			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Relpax with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of

marketed and unapproved drug products and a prescriptions for Relpax (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

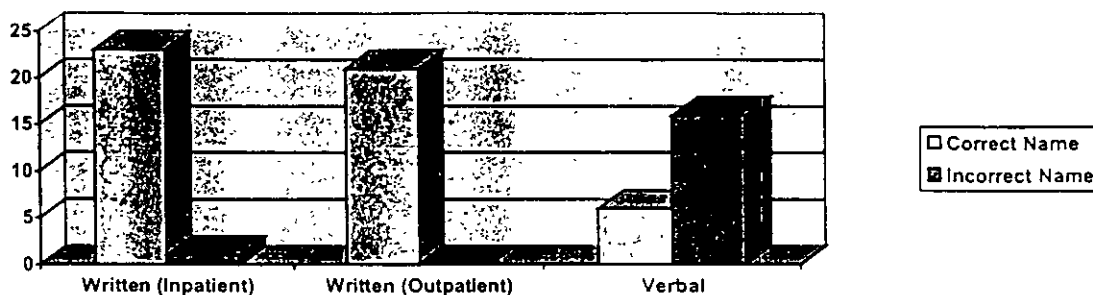
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p><i>Relpax 40mg</i> <i>Sig: 1 at onset, M Relpax</i> <i>2° pm</i></p>	<p>Relpax 40 mg One at onset...may repeat once in 2 hours as needed.</p>
<p><u>Inpatient RX:</u></p> <p>1/10/00 9:00 am Relpax 40mg 1 at onset HA MRX 1 #10 D. M. M. 0 100 as du #1</p>	

2. Results:

The results for Relpax are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%) "Relpax"	Incorrectly Interpreted (%)
Written Inpatient	39	24 (62%)	23 (96%)	1 (4%)
Written Outpatient	35	21 (60%)	21 (100%)	0 (0%)
Verbal	32	22 (69%)	6 (27%)	16 (73%)
Total	106	67 (63%)	50 (75%)	17 (25%)



Among participants in the written prescription studies, 1 of 45 respondents (2%) interpreted the name incorrectly. The interpretations were misspelled variations of "Relpax". The incorrect interpretation of a written prescription was *Repax*. This interpretation is not similar to any drug product currently marketed in the United States.

Among participants in the verbal prescription studies, 16 of 22 (73%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of "Relpax". Incorrect interpretations of the verbal prescription included: *Realtex*, *Reltex* (3 occurrences), *Rel-Pack*, *Roltax*, *Railpax*, *Relpack* (4 occurrences), *Relpac* (2 occurrences), *Relapac*, *Relpak* and *Relpaks*. The interpretation, "Reltex" bears some sound-alike similarity to the marketed drug product Valtrex.

C. SAFETY EVALUATOR RISK ASSESSMENT

I. Look-alike/Sound-alike Name Concerns

In reviewing the proposed proprietary name "Relpax", the primary concerns raised related to look-alike, sound-alike confusion with names already in the U.S. marketplace. The products considered to have potential for name confusion with **Relpax** were Relafen, Raplon, and Valtrex. Although Raplon was mentioned by the DMETS Expert Panel, the potential for confusion is minimal based on the differences between the drug products and the fact that the drug is no longer marketed. Raplon and Relpax differ in dosage form, route of administration, strength, and indications.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Relpax can be confused with Relafen or Raplon. However, the interpretation, "Reltex" bears some sound-alike similarity to the marketed drug product Valtrex. The majority of interpretations from the written and verbal prescription studies were phonetic/ misspelled interpretations of the drug name Relpax.

Relafen is the proprietary name for Nabumetone Tablets. Relafen Tablets are indicated for acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis. The recommended dose of Relafen Tablets is 1500 mg to 2000 mg daily either in a single or twice-daily dose. Relafen and Relpax may look alike when scripted (see writing sample on page 6).

The word "Relpax" is handwritten in a cursive style. The letters are connected, with a prominent 'R' and 'p'.The word "Relafen" is handwritten in a cursive style. The letters are connected, with a prominent 'R' and 'f'.

The first syllable of each name "Rel" contribute the greatest to this name pair's look-alike properties. The "p" in Relpax may also look like the "f" in Relafen. In addition, both products are oral tablets which may be taken once or twice a day. Despite look-alike similarities, Relpax and Relafen have differences which make them distinct from each other. Relpax will be available blister card packaging and will be dispensed with patient information regarding its use. Relafen does not have a patient information leaflet and is not commercially available in special packaging. Patient information available for Relpax will be a barrier to confusion between these products. Also, these products do not share a common strength. Relafen is available in 500 mg and 750 mg tablets while Relpax will be available in tablets of 20 mg, 40 mg, and 80 mg. Since each product has multiple strengths, prescription orders inadvertently omitting the strength will most likely be clarified by the pharmacist. A distinction can also be made for the dosing schedule of these drug products. While Relafen is to be dosed on a regular schedule, once or twice daily, Relpax is only dosed when needed for migraine headache. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between the medications including strength, dosing schedules, and packaging, and due to lack of convincing look-alike similarities.

Valtrex is the proprietary name for Valacyclovir Hydrochloride Tablets. Valtrex is indicated for the treatment of herpes zoster (shingles) and for the treatment or suppression of genital herpes. The recommended dose of Valtrex is 1 gram 3 times a day for 7 days for herpes zoster, 1 gram twice daily for 10 days for genital herpes, and 500 mg to 1 gram daily for suppressive therapy of recurrent genital herpes. Valtrex and Relpax may sound alike when spoken. Each name has two syllables. Sound alike similarity in the first syllable of each name can be attributed to the phonemes "al" vs. "el". In the second syllable sound alike characteristics may be attributed to phonemes "ex" vs. "ax". Despite sound-alike similarities, Valtrex and Relpax have differences which make them distinct from each other. Relpax will be available blister card packaging and will be dispensed with patient information regarding its use. Valtrex does not have a patient information leaflet and is not commercially available in special packaging. Patient information available for Relpax will be a barrier to confusion between these products. Also, these products do not share a common strength. Valtrex is available in 500 mg and 1 gram tablets while Relpax will be available in tablets of 20 mg, 40 mg, and 80 mg. Since each product has multiple strengths, prescription orders inadvertently omitting the strength will most likely be clarified by the pharmacist. A distinction can also be made for the dosing schedule of these drug products. While Valtrex is to be dosed on a regular schedule, Relpax is only dosed when needed for migraine headache. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between the medications including strength, dosing schedules, packaging, and a lack of convincing sound-alike similarities.

2. Concerns of Confusion with "Packs"

Some members of the expert panel expressed concerns that this name could be either confused with other drug names that are associated with "packs". The table below lists some drug products which have "pack" or a modification of that word in their name.

Proprietary Name	Established Name	Drug Class
Z-Pak (Zithromax)	Azithromycin Dihydrate	Antibiotic
Teq-Paq (Tequin)	Gatifloxacin	Antibiotic
Omni-pac (Omnicef)	Cefdinir	Antibiotic
Avelox ABC Pack	Moxifloxacin	Antibiotic
Cipro Cystitis Pac	Ciprofloxacin	Antibiotic
Biaxin XL-Pac	Clarithromycin	Antibiotic

The risk of dispensing the wrong medication should be low due to lack of convincing sound-alike or look-alike similarities between Relpax and the above drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels (heat sealed card), package insert, professional sample, carton, starter kit, and patient information labeling of Relpax, DMETS has focussed on safety issues relating to possible medication errors and has identified several areas of possible improvement, which might minimize potential user error.

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IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Relpax.
2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Hoppes
12/4/02 03:22:43 PM
PHARMACIST

Carol Holquist
12/4/02 04:23:26 PM
PHARMACIST

Jerry Phillips
12/5/02 07:32:00 AM
DIRECTOR

Chen, Lana Y

From: Bastings, Eric
Sent: Friday, December 20, 2002 6:57 PM
To: Chen, Lana Y
Cc: Oliva, Armando
Subject: RE: IMPORTANT: New Demographic Worksheet for NME approval action packages

Here is the demographic worksheet.

I used the original NDA review to fill in the numbers.

I could not easily identify how many women over 50 participated in the phase2/3 studies, so I left that field empty.

I filled the others fields the best I could.

Happy Holidays.



relpax demo.doc

Eric

-----Original Message-----

From: Chen, Lana Y
Sent: Friday, December 20, 2002 3:21 PM
To: Bastings, Eric
Subject: FW: IMPORTANT: New Demographic Worksheet for NME approval action packages

-----Original Message-----

From: Locicero, Colleen L
Sent: Friday, December 20, 2002 3:19 PM
To: Chen, Lana Y
Subject: FW: IMPORTANT: New Demographic Worksheet for NME approval action packages

Here it is.

-----Original Message-----

From: Jenkins, John K
Sent: Monday, July 01, 2002 4:36 PM
To: CDER-OND-ALL
Cc: Woodcock, Janet; Galson, Steven
Subject: IMPORTANT: New Demographic Worksheet for NME approval action packages

This message is directed to all OND medical officers and project managers, including team leaders and supervisors. Others on the distribution list may disregard this message. The demographic worksheet will be required for all NME approval action packages beginning July 15, 2002. The text below provides background on the development of the demographic worksheet along with instructions on how to complete the form and where to obtain additional information. I thank you in advance for your attention to this important matter and your compliance with the procedures outlined below.

In a final rule published February 11, 1998 (effective August 10, 1998), FDA amended 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. The final rule also noted that we have the authority to refuse to file an application under 21 CFR 314.101(d)(3) if there is "inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets."

To address issues associated with this Rule, the Women's Health Subcommittee (of the MPCC) developed a demographic worksheet. Development of the worksheet included presentations and discussions at MPCC

(10/98, 3/99, 5/01), Division Directors' Policy (7/99, 9/99) and a pilot program in ODE 1. In July 2001, the GAO published a report recommending that the "FDA adopt management tools that will ensure drug sponsors' compliance with current regulations regarding the presentation of data by sex and that its reviewers' consistently and systematically discuss sex differences in their written reviews of NDAs."

If you have questions regarding this worksheet, please contact Kim Colangelo (colangelok or 594-5400).

<< File: instructions1.doc >> << File: worksheet1.doc >>

Chen, Lana Y

From: El Hage, Jeri D
Sent: Tuesday, December 17, 2002 11:29 AM
To: Chen, Lana Y
Subject: FW: NDA 21-016 for Relpax (eletriptan hydrobromide)

FYI. Sorry I forgot to include you on the original Email.

Jeri

-----Original Message-----

From: El Hage, Jeri D
Sent: Tuesday, December 17, 2002 11:17 AM
To: Lodicero, Colleen L; Benton, Sandra J
Cc: Rosloff, Barry N
Subject: NDA 21-016 for Relpax (eletriptan hydrobromide)

Colleen,

I have looked at the approval letter and labeling for the Relpax NDA that you forwarded this morning. The pharm/tox sections of the labeling look fine as written. Since there were no outstanding pharm/tox issues or no new data provided on this review cycle, I have no comments and do not plan to write a memo.

Jeri

Demographic Worksheet

Application Information (Enter all identifying information for the submission pertaining to this summary)

NDA Number: 21-016

Submission Type: N/A (pilot)

Serial Number: N/A (pilot)

Populations Included In Application (Please provide information for each category listed below from the primary safety database excluding PK studies)

CATEGORY	NUMBER EXPOSED TO		NUMBER EXPOSED		NUMBER EXPOSED	
	STUDY DRUG		To STUDY DRUG		To STUDY DRUG	
Gender	Males	769	All Females	4263	Females >50	
Age	0-≤1 Mo	0	>1 Mo.-≤2Year	0	>2-≤12	0
	12-16	274	17-64	4708	≥65	50
Race	White	4786	Black	154	Asian	28
	Other	64				

Gender-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on gender recommended in the label?

If the analysis was completed, who performed the analysis

Was gender-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

☐ Yes

☒ No

☒ Sponsor

☐ FDA

Age-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on age recommended in the label?

If the analysis was completed, who performed the analysis

Was age-based analysis included in labeling?	
YES	No
<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>

☒ Yes

☐ No

☒ Sponsor

☒ FDA

Race-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on race recommended in the label?

If the analysis was completed, who performed the analysis

Was race-based analysis included in labeling?	
YES	No
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

☐ Yes

☒ No

☒ Sponsor

☐ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment: